Technology
Arts Sciences
TH Köln

UNIKLINIK
KÖLN

Master's Thesis

Evaluating an Approach for mapping FHIR Profiles to Research Protocols

Markus Döring, B. Sc - 11095756

Faculty:	F10 - Informatik und Ingenieurwissenschaften
Field of study:	Master Computer Science - Software Engineering
Supervisor:	Prof. Dr. Heide Faeskorn-Woyke
External examiner:	Benjamin Nowack
Company:	Medical Systems R&D Clinical Trials Center Cologne Dpt. I for Internal Medicine | Prof. O. A. Cornely, Prof. M. Hallek University Hospital Cologne
Date:	August 16, 2018

Declaration of Originality

I confirm, that this thesis is my original work and that I have referenced all sources used in the work.

Furthermore, I confirm that:

- this work has been composed by me without assistance.
- I have referenced by, departmental requirements - in both the text and the bibliography or references - all sources (either from a printed source, internet or any other source) used in the work.
- all data and findings in the work have not been falsified or embellished.
- this work has not been previously, or concurrently, used either for other assignments or within other exam processes as an exam assignment.
- this work has not been published.

I confirm that I understand that my work may be electronically checked for plagiarism by the use of plagiarism detection software and stored on a third party's server for future comparison.

Gummersbach, August 16, 2018

Markus Döring

Confidential Content

This master's thesis contains confidential data of the Medical Systems R&D group at the University Hospital of Cologne.
This work may only be made available to the first and second reviewers and authorized members of the board of examiners. Any publication and duplication of this thesis - in part or whole - is prohibited, unless Medical Systems R&D gives explicit permission.
An inspection of this work by third parties requires the expressed permission of the author and the Medical Systems R&D.

Abstract

Observational studies and clinical trials have become increasingly important over recent years and play an essential role in advancing medical knowledge. In today's world of clinical research, it is not possible to imagine trials without the foundation of a well-established it-infrastructure. Electronic capture and usage of data is pervasive.

In practice, medical progress requires the ability to integrate data from different systems. An essential factor in enabling different actors, such as institutions and hospitals, to have their systems exchange structured data and make use of the information is the interoperability of the data and systems.

FHIR (Fast Healthcare Interoperable Resources) is a free and easily customizable HL7 platform standard, based on 30 years of experience of HL7. It is focused on providing health-related information and defines a set of capabilities used in the health care process.

This thesis will provide a conceptual approach for working with FHIR, as well as concrete approaches for working with FHIR profiles and for customizing the standard for particular use cases. It will be carried out in cooperation with the Medical Systems R&D, which is a service provider within the University Hospital of Cologne.

The guiding request approach will focus on the evaluation of requirements for clinical trials and how clinical research protocols can be represented in an interoperable and machine-parsable format using FHIR.

Keywords:
Interoperability; FHIR; Medical Knowledge; Health Care; Clinical Trials; Research Protocols

Contents

Acknowledgements

The present master's thesis was created as part of my computer science degree with the core focus on software engineering.

My interest in interoperability, especially in the context of FHIR, started with two guided projects at the Cologne University of Applied Science. During that projects, our team redesigned and extended a functional FHIR-Server in cooperation with telexiom AG. Though the projects focused on technical implementation, they got me interested in the conceptual approaches to interoperability in the medical field - especially with regards to the groundbreaking role that FHIR was playing there.

During our presentation at the FHIR Dev-Days 2017 in Amsterdam, we made several contacts with companies and research groups working with FHIR and interoperability. The idea for the subject of this thesis was elaborated in a personal meeting with Gustav Vella, team lead of the Medical Systems R&D at the University Hospital of Cologne. We discussed their present work on the convergence of Health care and Clinical Research and the fundamental role FHIR was playing - specifically with regards to Clinical Trials. This meeting resulted in the idea that I should evaluate an approach for mapping clinical research protocols to FHIR resources.

At this point, I would like to thank Gustav Vella for introducing me to clinical trials and providing the working environment and guidance during the project.

Furthermore, I owe thanks to my supervisor at the Cologne University of Applied Science, Prof. Dr. Heide Faeskorn-Woyke. It was she who started the guided projects related to FHIR which led to our presentation and award at Dev Days 2017. She also accepted my suggestion to keep on working in this area for the master's thesis. She offered her guidance, not only during the meetings but also while writing excerpts of this thesis.

Last but not least, I would like to say thank you to everyone who supported me during the project and on writing this thesis.

Gummersbach, August 16, 2018
Markus Döring

1. Introduction

1.1. Motivation

Over the last years, health care providers have come under increasing pressure to provide a better service at lower costs. Compensation is increasingly based on treatment-quality and results (Pay4Performance). At the same time, innovative therapies involve highly specialized testing and continuous intersectoral documentation.

While only a few years ago, the primary goal of medical documentation was to satisfy legal requirements, today the goal of data-driven treatment is of at least of equal importance. Also, an increase in clinical research, in the interest of the patients, is placing new requirements on the quality of medical documentation.

Innovative therapies involve personalized and genomic medicine which take into account a vast amount of data a specialized documentation which has to be linked up to routine documentation in the Electronic Medical Record. [1]

However, present clinical systems and the routine data collected don't have the quality needed to ensure a safe therapy assessment or to support prospective long-term studies.

This is the reason why individual and highly specialized systems are evolving. These Systems, however, do not integrate well with the primary systems. This is due to the high barrier in supporting legacy interoperability standards but also due to the fact that these standards do not yet support the semantic models for these innovative new domains. The electronic medical record is highly fragmented, and the user needs to access multiple decoupled systems. Solutions using a typical data warehouse are a possible approach to integrate the data, but it still doesn't help the challenges regarding the quality of data because optimal documentation can only be achieved in the clinical context. [2]

Additionally, data warehouse approaches have proven to be expensive in acquisition, establishment, and maintenance. The costs for IT are high since new interfaces have to implemented and maintained constantly and consistently. For medical personnel, the effort is high too, since the data has to be transformed outside of the clinical context.

Based on the insight, that the quality of data and the efficiency in its aggregation is dependent on its integration of clinical processes, a solution for a better documentation can only be reached in the clinical context.

A prerequisite towards this goal is standardization of data, transport-formats and application interfaces.

Such a standard is the Fast Healthcare Interoperability Resources standard (in short FHIR) which is currently emerging internationally and has gained high popularity. It is created, published and maintained by the HL7 community [3].

The integration, described above, and the structured input and output are made possible by this standard. It combines format, transport, and interfaces into a framework, that is still compatible with other protocols, such as HL7 v2 and IHE.

FHIR is bringing to health care a paradigm shift, from document-centered approaches to direct access to granular data fields. "FHIR represents clinical data as resources, where each resource is a coherent expression of meaning stated in terms of well-defined fields and data types.". [4, p.900] An essential goal of FHIR is, to enable the processing of health care data on mobile devices such as smartphones and tablets and to integrate them with existing systems.

The FHIR Standard builds on existing web-based interfaces and provides security mechanisms, to accomplish the high data safety and privacy requirements needed in health care.

This technology is enabling the granularity and quality needed for data-driven clinical decisions and innovative clinical research.

1.2. Research Approach

The main goal of this thesis is to develop an approach where researchers can move on from writing clinical protocols in a document-centered format to a format which is directly accessible in a machine-readable pattern.

The advantages are numerous. For one, the protocols - which could be highly complex - can be validated to avoid costly inconsistencies. Also, they could be deployed in various systems for different purposes - for instance, monitoring compliance or planning treatment schedules at the study site.

To give some insight into the complexity of a study protocol we consider the following:

Patients will be recruited in a time frame of 6 to 12 months depending on how difficult it would be to reach the sample size for the trial. The visit schedule would be defined for each patient relative to their date of enrollment. Any delay in the treatment would - from the point of view of the trial - only be tolerable to a certain extent. If the subject has an infection or any other adverse event, one would have to wait until the study subjects are in a state to continue treatment with the investigational drug. Within a tolerable delay, you would reset the schedule for the following visits relative to that delay.

The delay has a tolerable range "Allowable Window": if the patient delays too long - depending on the trial - they'd would fall out for the major statistical analysis and would remain in the trial with the "Intent to Treat". The allowable windows of delay in the schedule may be different for each investigational drug in the same trial.

Treatment noncompliance may have consequences for the further treatment. For example, it would possibly no longer make sense to have the patient endure a painful bone marrow biopsy at final assessment (last visit of the treatment phase) once the patient is no longer fully compliant with the regimen/study protocol.

Presently systems have to model and calculate the allowable windows for all visits within the individual applications for each trial. It would make sense for the researcher writing the protocol to publish that data in FHIR for systems to import and avoid the burden and possibility of errors.

1.3. About the Medical Systems R&D group

The Medical Systems R&D group, supporting this thesis have cooperated with the author by sharing their knowledge and previous work. Medical Systems R&D is a research group and service provider for clinical research at the university hospital in Cologne.

The history of the group was from my point of view fascinating because it gave me insight into what it takes to set up a group to develop qualified medical software from scratch. Information used for this chapter were obtained in personal communication. [5]

The group was set up in 2010 as a joint group of the Clinical Trials Center Cologne and the German CLL Study Group with the purpose of developing innovative software for conducting clinical trials. To ensure software qualification, a joint structure was required, and it was agreed that an informal joint group would be set up.

A Quality Management System (QMS) was set up with the help of external consultation. An employee dedicated to Requirements Management (REQM) and Software Quality Assurance (SQA) was engaged in 2011. In line with the goals of all parties to conduct high-quality clinical research, the envisaged systems were originally planned to satisfy the following quality requirements:

- ICH Topic E6, Guideline for Good Clinical Practice, 1997
- German Pharmaceutical Law, AMG, implementing GCP-V, 2004
- Laws on patient data protection and personal data privacy (Datenschutzgesetz Nordrhein-Westfalen - DSG NRW) as per bulletin of 9th of June 2000

The development and system specifications have in the course of the project also taken the following guidelines into account:

- 21 CFR part 11
- European Medicines Agency, Reflection Paper on expectations for Electronic source data transcribed to electronic data collection tools in clinical trials, 2007
- FDA, General Principles of Software Validation, Final Guidance for Industry and FDA Staff, 2002
- FDA, Guidance for Industry, Computerized Systems Used in Clinical Investigations, 2007
- Martin and Perez, GAMP 5 Quality Risk Management Approach, 2008
- Eudra Lex, Volume 4, Good Manufacturing Practice, Annex 11: Computerized Systems, 2011
- Relevant QM- and Process-Management norms such as ISO 9000, ITIL

The setup of the new group and processes led to the successful development of a pilot version of a Clinical Data Management System in December 2011, a successful vendor audit in April 2012 and a production release of a basic GCP compliant system in May 2013. A successful User Acceptance Test (UAT) by DCLLSG led to the formal commissioning of the system for the CLLM1 Trial in June 2013. An informal charter was set up in 2011. It has been elaborated on overtime by the feedback of stakeholder meetings/executive meetings.

Systems R&D pursues the primary purpose of developing innovative systems and services to support clinical research. To this goal, a set of fundamental values was defined. Quality and usability standards will be of utmost importance and will drive all work SRD sets out to engage in. SRD also strongly believes in a close relationship with the individuals and institutions commissioning and using its systems or services. It considers the relationship to be its major asset and will continuously strive to strengthen this relationship by anchoring it in its processes and strategies. Accountability and a focus on solutions are part of this strategy.

The primary stakeholders, Michael Hallek and Oliver Cornely, themselves deeply engaged in clinical research, have set up the group committed to the stated values and have entrusted their research and funds in the ability of the group to perform on these values.

1.4. Structure of the Thesis

The Thesis starts off with a theoretical explanation about interoperability in the specific context of FHIR (chapter 2.1). The different stages of interoperability follow an introduction to the history of HL7 (chapter 2.2). Different examples and the concrete meaning of each layer in FHIR are given; focused on building a general understanding of interoperability and the possibilities it enables.

This is followed by an insight into clinical studies and clinical protocols (chapter 2.3). The focus here is set on the techniques and procedures of Systems R&D, even though these principles and technologies are found in similar ways in other companies and institutions; meaning they can be generalized to a certain point as well.

Clinical trials are a very complex subject, and different aspects can be discussed. Since this thesis can't cover all possible points, the explanations are limited to the sections which are necessary for understanding the approaches described.

The customizability of FHIR is shown, starting with an explanation of the hierarchy of resources (chapter 3.1.2), followed by limits and scopes of profiling (chapter 3.2). This includes some central aspects of profiling but does not cover all possible aspects. The approach taken is to build FHIR profiles, based on the standard patterns used in clinical care and extend these to be able to cover clinical protocols (chapter 5). This approach is discussed and applied with the background knowledge and infrastructure of Medical Systems R&D. Even though the technical approaches and the Systems are internal and protected, the FHIR profiles are free to use and can be taken into consideration for further strategies.

The thesis finishes off with an explanation of the lessons learned during the project (chapter 6.1). Including the positive and negative aspects, as well as a personal opinion of the author. A final future outlook wraps up the thesis and shows the possibilities for continuing the project and creating machine-readable clinical trial protocols (chapter 6.2).

2. Theoretical Background

This background is intended to provide a basis for understanding the context and solution approaches which have been elaborated on as part of this thesis. It deals with the origins of interoperability, and the standards organization HL7, as well as HL7 FHIR and its origins.

A considerable challenge these days is the communication between different Stakeholders in health care and their respective systems. As electronic data and health care IT Systems have become highly specialized in the recent years, various stakeholders have developed their technology in an isolated way. The different Systems have continued to exist and evolved independently, creating a communication gap. [6] Most recently, the focus has shifted to integrating these specialized systems with the electronic health record (EHR).

Interoperability is the technical solution for this communication gap. There are various reasons for making an effort to achieve interoperability in health care. These reasons include, but are not limited to:

1. Less burden and improved patient satisfaction, avoiding unnecessary double testing.
2. Faster diagnostics using data from different institutions in aggregated and possibly filtered form; resulting in less manual work for the practitioner.
3. An overall better general view of the patient's clinical data, resulting in higher clinical safety

Consequently, if no interoperability is achieved, harmful and risky situations can arise in the clinical context, which in the best case would only lead to significantly higher costs, in the worst case to wrong treatment decisions. [7]

It is often stated in the literature, that a patient should not only be seen as an expense factor but that the focus and attention should be on achieving a "value" for the patient. [8]

To realize this up to a certain level, different layers of interoperability which build upon each other have evolved. [9] A more detailed explanation of the different layers can be found in chapter 2.1.

Since the goal is to work out a feasible connection between FHIR and research protocols, this chapter as the thesis in general mainly focuses on Fast Healthcare Interoperable Resources (FHIR). It is an evolving Standard, and Systems R&D has as of adopted the use of FHIR in their Systems over the last year an a half. A more detailed overview of FHIR is given in Section 2.2.

Also, some background on clinical trials and how they are conducted on clinical sites will be necessary (Section 4).

Here, we will focus on a subset of the clinical protocol data based on concrete examples in projects of Systems R&D and the University Hospital Cologne.

The University Hospital of Cologne historically has a strong focus on Clinical Trials. It hosts the oldest Academic Study Group in Germany - the German Hodgkin Study Group (GHSG) and the very successful German CLL Study Group (GCLLSG) [10]. The hospital is one of the primary study sites in Germany conducting up to 700 clinical Trials per year [11].

2.1. Interoperability

A central element in the digital world of health care is the possibility of sharing data and information in a timely and secure manner between patients, hospitals, dispensaries, health insurances and other clinical institutions. However, the present electronic exchange of information doesn't provide this kind of communication. A prerequisite is that the sender and receiver both understand the data and can process the information.

To accomplish this, multiple international standards have evolved in the recent years. A few examples are *SNOMED CT, HL7, HL7 FHIR, DICOM* and *LOINC* [12].

The ability to exchange and share information in health care is often seen as "essential to facilitate the quality and effectiveness of health care services" [13] Interoperability is often referred to as the ability of different systems to exchange data and use information that has been transferred. HIMSS states "Interoperability means the ability of health information systems to work together within and across organizational boundaries to advance the health status of, and the effective delivery of health care for, individuals and communities." [14]

Another common definition for Interoperability is the "ability of two or more systems or components to exchange information and to use the information that has been exchanged". [15]

In practice, this would, for example, mean that observations of a patient made at a specialists practice can be transferred to a hospital and be processed further, for example in the "electronic medical record" (EMR) of that hospital.

In general terms, different steps have to be fulfilled, if a system wants to be interoperable. These steps might seem trivial but are necessary to construct an interoperable digital medical record. [16]

1. The medical information needs to be represented in a digital form, to enable a lossless electronic transport of the data.
2. The Electronic Health Records (EHRs) need to have the capability to transfer the information to other systems digitally.
3. The receiver of the information must be capable of understanding and processing the information, as well as integrating multiple records. [16]

The Article of Diameter Health states further that the third step of achieving interoperability is the hardest since it deals with *semantic interoperability*. It is one of the layers that are commonly used to classify interoperability. However, there is no consensus about the number of levels. Some authors define three; others chose a four or higher tier model (figure 1). [17] [18]

We can take *HL7 FHIR* as an example to show the defined levels of interoperability.

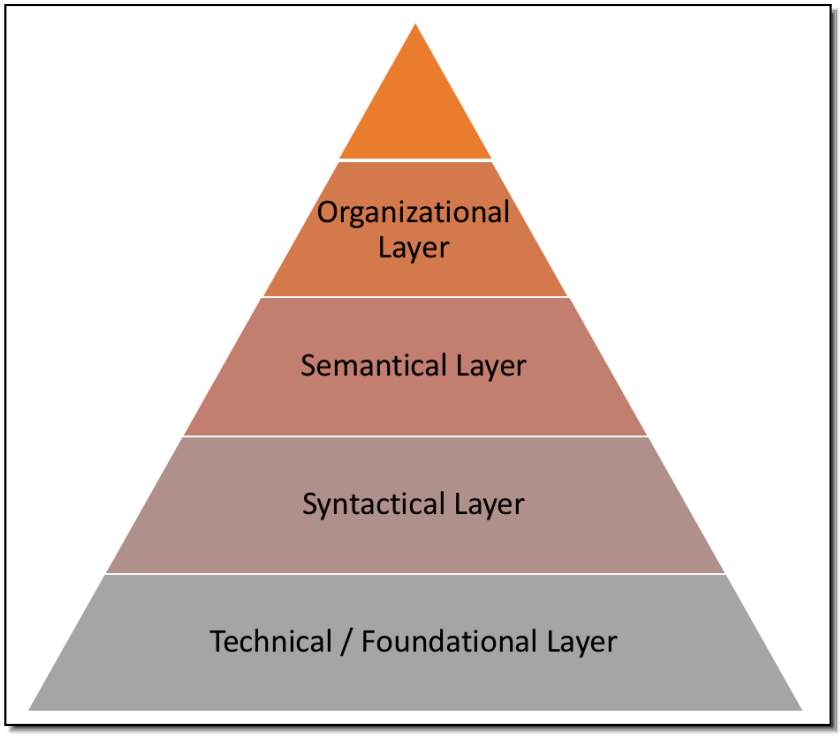


Figure 1: Levels of interoperability (adapted from [19])

1. **Technical / Foundational interoperability**
   Technical Interoperability is often called Foundational Interoperability. It refers to the connectivity between the communication and information systems, which are involved in the exchange of data. It describes the possibility to build a network of systems, based on a chosen communication protocol. [20]

2. **Syntactical interoperability**
   As a verification of the structure, syntactical interoperability can be taken into account. It can be described as a model, that can be used to measure if specific aspects of the data are encoded correctly. The validation can include content, data types and other validation rules. [21]

3. **Semantical interoperability**
   As opposed to other domains, such as banking, where the resources are quantifiable, and the information is highly structured, health care data most likely isn't. Physicians may document the same analysis in different ways. Coding Systems like SNOMED CT[1] can help to achieve semantical interoperability since the descriptions can be done through code instead of free text. [16]

4. **Organizational interoperability**
   The highest level of interoperability is the so-called, organizational Interoperability. It facilitates the integration of business processes, as well as workflows beyond the boundaries of a single organization. It, however, needs a high level of commitment, since it requires the other three levels to collaborate. [13]

To sum up, it can be stated, that interoperability enables more efficient access to patient information and it can reduce the redundant collection of health care data [22].

Though many different standards can be used to achieve a defined level of interoperability, FHIR is the one that is focused on in this thesis. Systems R&D sees this standard as a vital step in bridging Clinical Research with Health care - domains which are today highly split causing unnecessary financial burden and slowing turnaround in clinical research. Several important companies such as Google [23], Apple [24] and Microsoft [25] have just recently adopted the standard.

[1] SNOMED is an international coding system about health care data, more information at https://www.snomed.org

2.2. FHIR

In the following Subchapter, Fast Healthcare Interoperable Resources (FHIR) is explained in further detail. We will do so sufficiently as to provide the necessary context for the concepts discussed in the thesis. In essence, the capabilities of customizing existing resources (chapter 2.2.2) will have to be understood in sufficient detail.

For completeness, at the time of this thesis the applicable FHIR release is version 3 (Standard for Trial Use). Therefore, all explanations refer to this version. Experimental work on future versions will be referred to in the future outlook section (chapter 6.2).

2.2.1. History of HL7 and FHIR

The HL7 Organization, the publisher of FHIR, dates back to the late 1970s. The University of California first published it in San Francisco (UCSF). HL7 v1 and v2 are sometimes called refinements of the UCSF protocol [26].

A big issue at the time was that all interfaces between systems were exchanging data using custom solutions. Each of them designed individually and the sending and receiving of data resulted in manual work on each side of the sender and receiver [27].

Solving this problem by using a standard in health care, it was deemed essential to determine stakeholders, who have an interest in the whole system. In the Context of HL7, different user types have emerged. These users have an equal influence on how a standard is developed and used in health care. These three groups are actively interested in HL7 Standards and can be described as follows [27]:

1. **Clinical interface specialist**
   This user group is responsible for transferring data between different institutions. They are tasked to move the clinical data or create clinical applications for exchanging data with other systems.
2. **Government or other politically homogeneous entities**
   The biggest interest here is the future of sharing data across different institutions. Sometimes this group is even looking to move data into new fields, which are not yet covered by an interoperable working system.

3. **Medical Informaticists**

   Are working in the field of health informatics. This group seeks to understand clinical knowledge and build up an ontology[2]. This persona is interested in the general representation, semantic interoperability and the modeling of actions and actors in health care.

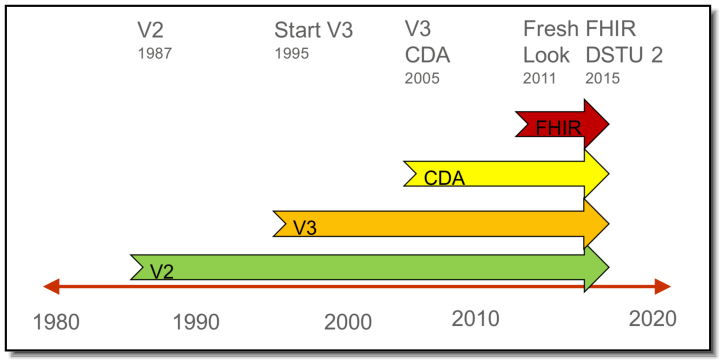


Figure 2: Timeline of HL7 Standards [28, p.17].
Licensed by CC BY 3.0

The HL7 v2 Standard was initially published in 1989 after a proof-of-concept completed in 1987 [29]. This Version sets the focus on the exchange of data through, so-called *segments*. They can be described as an ordered amount of data elements, used to transfer a bundle to a specified receiver.

A message in HL7 v2 has a concrete message type; besides, it is encoded by a specific message syntax table, which contains the metadata for the individual model. One single line of a message is called a *segment*. Taking the PatientName as an example, it is placed at the 5th position of PatientIdentification Details segment. The delimiters that separate different elements can determine the position. [18]

HL7 v2 is still widely in use, however, to help FHIR spread and evolve further, HL7 has provided mapping tables from different standards (including v2) to FHIR (table 5). Quoting Dr. Frank Oemig, a Senior eHealth Architect at Deutsche Telekom Healthcare and Security Solutions GmbH in Mülheim, a leading expert on HL7 V2:

HL7 v2 ist derzeit noch der am weitesten verbreitete Standard, er entwickelt sich konstant weiter und wird noch mindestens die nächsten 10 Jahre weiter genutzt. [30]

-

HL7 v2 is still the most used standard. It is constantly evolving and will be used for at least ten more years (free translation by the author of this thesis)

[2] A hierarchical structure, representing the knowledge about health care

Resource field	v2 Code
identifier	PID-3
active	
name	PID-5, PID-9
telecom	PID-13, PID-14, PID-40
gender	PID-8
birthDate	PID-7
deceased[x]	PID-30 (bool) and PID-29 (datetime)
address	PID-11
maritalStatus	PID-16
...	...

Table 1: Mappings for v2 to FHIR of the Patient Resource (adapted from [31])

Due to the high success of HL7 v2, the foundation decided to develop HL7 v3, as a direct successor. In addition, the Clinical Document Architecture (in short CDA) was created. In detail, CDA is a XML-based markup standard with the intend to specify encoding, structure and semantics of clinical documents, in order to exchange them. Both of those standards follow a model-driven design approach.

One of the most significant drawbacks in HL7 v2 is related to the missing information model that supports the structured and semantical setup of the messages. [32] [33] This results in the lack of possibility to represent some concepts such as medications and clinical workflows.

HL7 states, however, that the V2.x series of messages were widely successful and widely implemented. In fact, it's widespread use might also be the reason why V3 never took off. [34]

The Version 3 Normative Edition represents a new approach to clinical information exchange based on a model-driven methodology that produces messages and electronic documents expressed in XML syntax. [34]

Based on the RIM (Reference Information Model), the HL7 v3 Data Specification and the Vocabulary Specification, the information can be exchanged using the self-contained clinical documents (Clinical Document Architecture - CDA) or the XML-based messages of HL7 v3.

Due to the complexity of the HL7 v3 model, HL7 set out to create a new approach of using Resources. This provided the initial and fundamental concept for FHIR as it is right now. [35]

2.2.2. Layer of Interoperability in FHIR

As previously mentioned, FHIR is split into four different layers of interoperability (figure 1). FHIR describes their level of interoperability, without using the exact terms (technical, syntactical, semantical and organizational interoperability) (figure 3).

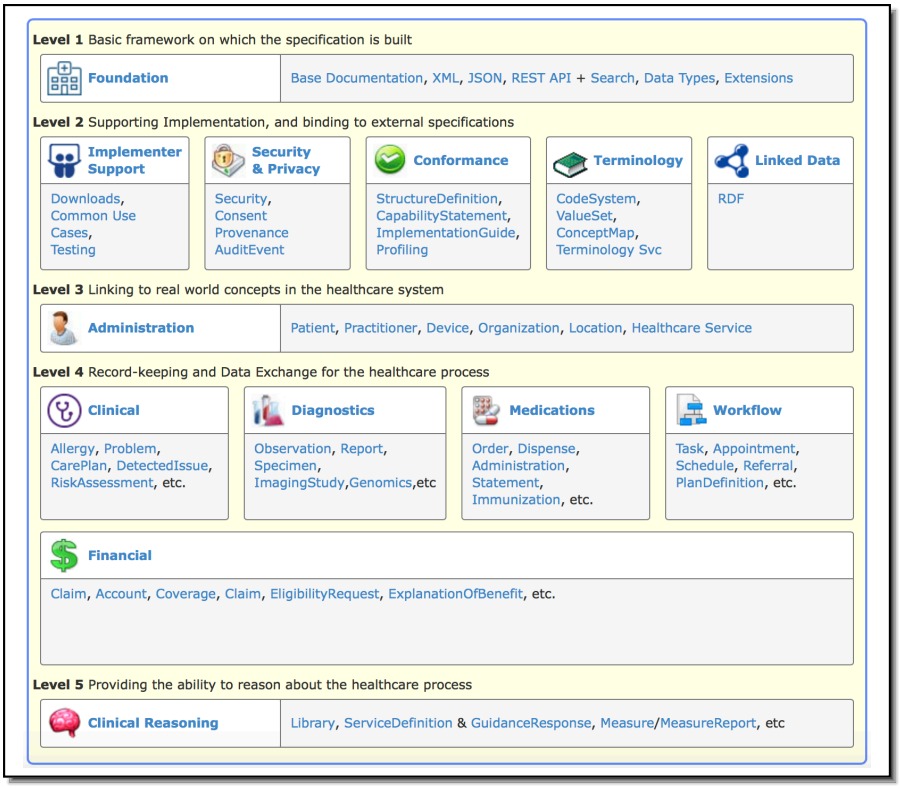


Figure 3: Layer of Interoperability in FHIR

Mapping the mentioned Levels of FHIR onto the four Layers of interoperability, we start with "**Level 1** Basic framework on which specification is built". This Level represents the technical interoperability, providing the necessary connectivity between the different systems. In FHIR the "Foundation Module" is responsible for the running infrastructure. [36]

Different techniques can be used to exchange the information on a technical Level. FHIR specifies four technologies:

1. **RESTful API**

   Most implementers are deciding to use the RESTful API as the connectivity method of their choice. According to the FHIR specification, it follows the principles of RESTful design for "Creating, Reading, Updating and Deleting" (CRUD-operations). [36]

   Though HL7 states, that FHIR is only supporting Level 2 of the REST Maturity model[3], Level 3 can be achieved through extensions. [37]

   Rest is performed in general directly through HTTP request and responses on the server. A few examples of different REST API calls in FHIR can be found in the appendix A.

2. **Messaging**

   The Messaging paradigm can be implemented using the RESTful API but also using any other form of a messaging stack. It allows the exchange of data using routing messages. Messages are triggered exclusively by clinical events, defined in the FHIR-Standard. They consist of a MessageHeader which indicates the type of the event, such as the destination of a possible response. The concrete procedures are not explained further at this point, because they are neither focus of, nor are they relevant for this thesis.[4][38]

3. **Documents**

   FHIR defines a computer-assisted human to human communication framework, to support the universal fact of having a human reader to communicate. To help ensure the confidentiality and the accuracy of the document, FHIR provides the possibility to create immutable versions of the report to work with[5].[39]

4. **Services / SOA**

   It has to be stated that all the alternatives above are "services" in some definition. SOA doesn't refer to an exchange format itself but indicating that basically, all exchange methods conform to the FHIR standard, as long as the exchanged data contains valid FHIR resources as in definition. Concluding, the FHIR-Specification allows and supports services like SOA to exchange data in the form of valid FHIR resources.[40]

[3]Further Information about the Maturity Model of the REST API can be found at https://martinfowler.com/articles/richardsonMaturityModel.html, written by Martin Fowler

[4]Further information about the messaging using FHIR Resources can be found here https://www.hl7.org/fhir/messaging.html

[5]Further information about the FHIR Documents can be found here https://www.hl7.org/fhir/documents.html

To support the syntactical interoperability, FHIR uses a conformance statement. This module represents metadata about the datatypes and resources used. The conformance resource contains two different statements. On the one hand, the ”ImplementationGuide” describes a set of rules that are used to solve a particular problem. The CapabilityStatement, on the other hand, can be described as a list, containing all the capabilities the FHIR-Server is supporting. [41]

According to the FHIR-Specification, the Server shall return the conformance resource on getting the particular request for it; displayed by the following URL.

http://providerserver/fhirbase/metadata

In this case, ”providerserver” is a placeholder for the URL of the provider and ”fhirbase” is representing the FHIR-Endpoint of the server. Calling metadata returns the Conformance-Statement, making it possible for external health care applications to automatically adjust their functions and capabilities to the ones of the FHIR-Server they are connecting with. [41]

An example Conformance Statement can be found in the appendix B.

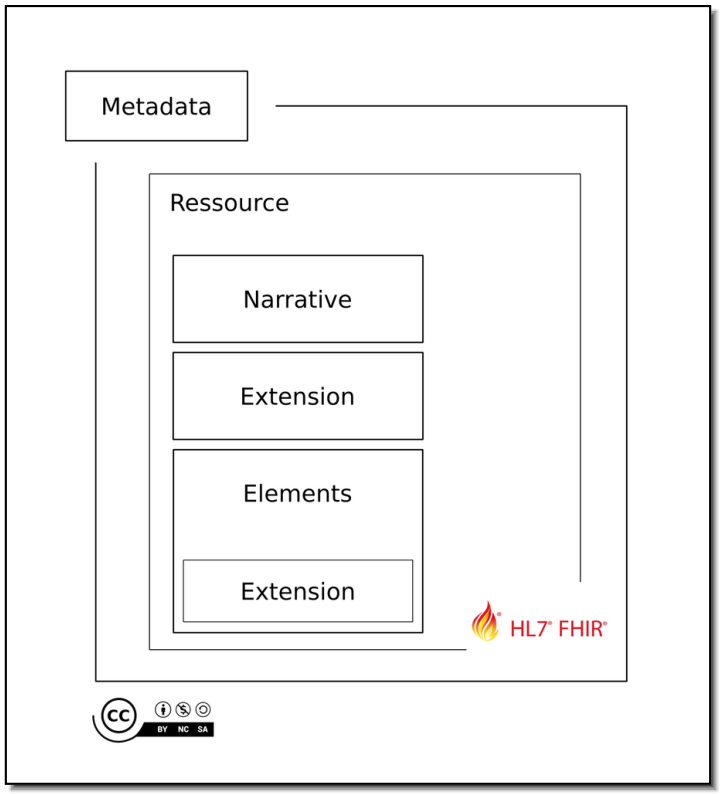


Figure 4: Components of a FHIR Resource [42]

The internal build of a FHIR Resource (figure 4) can be divided into different parts.

1. **Metadata**
   Metadata generally provides information about the content of an item. [43]

   In FHIR, Metadata contains the literal identity in the form of a URL and the date where the resource was last updated.

2. **Narrative**
   The narrative describes a representation of the resource that is human-readable. This is done to provide a base-level of interoperability since this representation of a resource should also be interpreted by a human.

3. **Elements & Extensions**
   Elements and Extensions are the part representing the actual data in FHIR. All necessary information is described in these sections of a resource. The Elements themselves are a normative part of in the standard, while the Extensions can be built individually by vendors or interested parties developing their specialized domains and applications. Further information on Extensions is given in chapter 3.

A single FHIR Resource itself can sometimes be not enough to represent the data needed for a certain Use-Case. To help this, FHIR provides the possibility to build up bundles of resources, linked by their literal or logical reference. Upon creation of a resource, the logical id is returned in the form of a Uniform Resource Identifier (URI). A resource should be obtainable by this URI, depicted in figure 5.

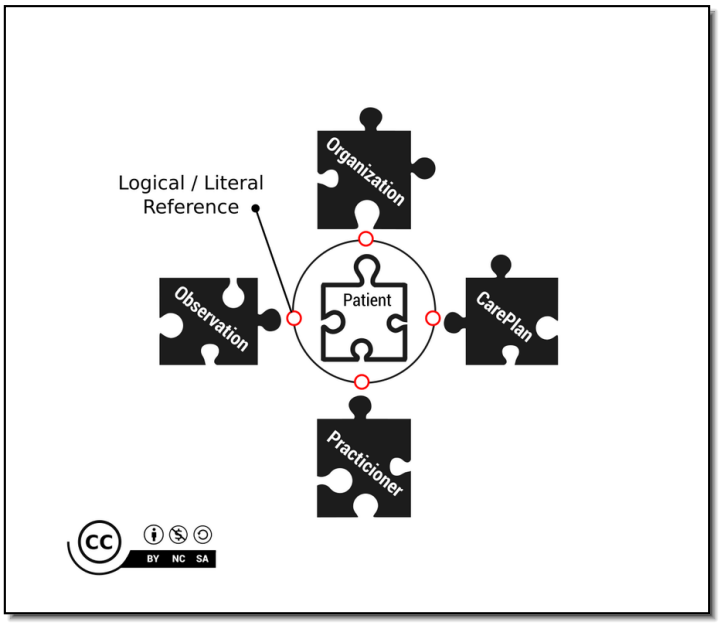


Figure 5: Linking FHIR Resources with Identifiers [42]

Building up a semantical understanding is fundamental in providing interoperability since the receiver of a message needs the ability of processing and understanding the message in a way, the sender intended (figure 6). To prevent misunderstandings, Coding-Systems like SNOMED CT provide external standardized terminologies. This results in elements, that are be machin-readable.

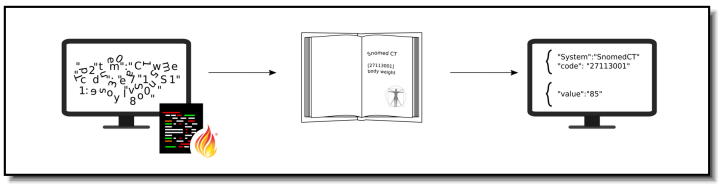


Figure 6: Using international Coding-Systems in FHIR [42]

In a specific Use-Case, it can be useful to refer to particular codes of the coding system. Using a ValueSet in FHIR, allows the possibility to only select out of a list of given codes.

The communication partners can ensure to have the same understanding of a single message and process as initially planned.

Lastly, FHIR also specifies *Organizational Interoperability*. It has to be stated that FHIR is a "Platform-Specification", which means that it enables concrete implementation on an international level. [44]

With the inclusion of, so-called, *extensions* and *profiling*, FHIR can enable cross-organizational communication on an interoperable level by reducing barriers.

This means that Resources can be modified, as long as the basic rules of the FHIR specification are matched. This includes cardinalities, data types, and ValueSets. More Information on organizational interoperability by using *profiling* is given in chapter 3.

2.2.3. Customizing FHIR to personal needs

Besides the base FHIR specification, which describes a set of resources, frameworks, and APIs, further adaptations in the form of customization are possible and common practice. These adaptations can be rules about resources, which define which elements are used and not used. Also, they can specify additional items added to resources that are not part of the base specification. [45]

The standard international resources that FHIR offers can be customized to fit the needs of a specific use case. Standardization in FHIR can be broken down into three different layers: (inter)national, regional and local levels. [46]

More detailed information about profiling is given in chapter 3.

2.3. Clinical Trials and Research Protocols

Clinical trials can be described as research studies with the goal of exploring whether a particular testing method or intervention (be it a medication, a new device or a particular treatment) is eligible for the medical use on human patients. Trials are one of the final obstacles, usually after a long process of basic research, in bringing a device or substance to the market. The process often starts in the laboratory moving on to animal testing (this phase is called "pre-clinical research/studies").

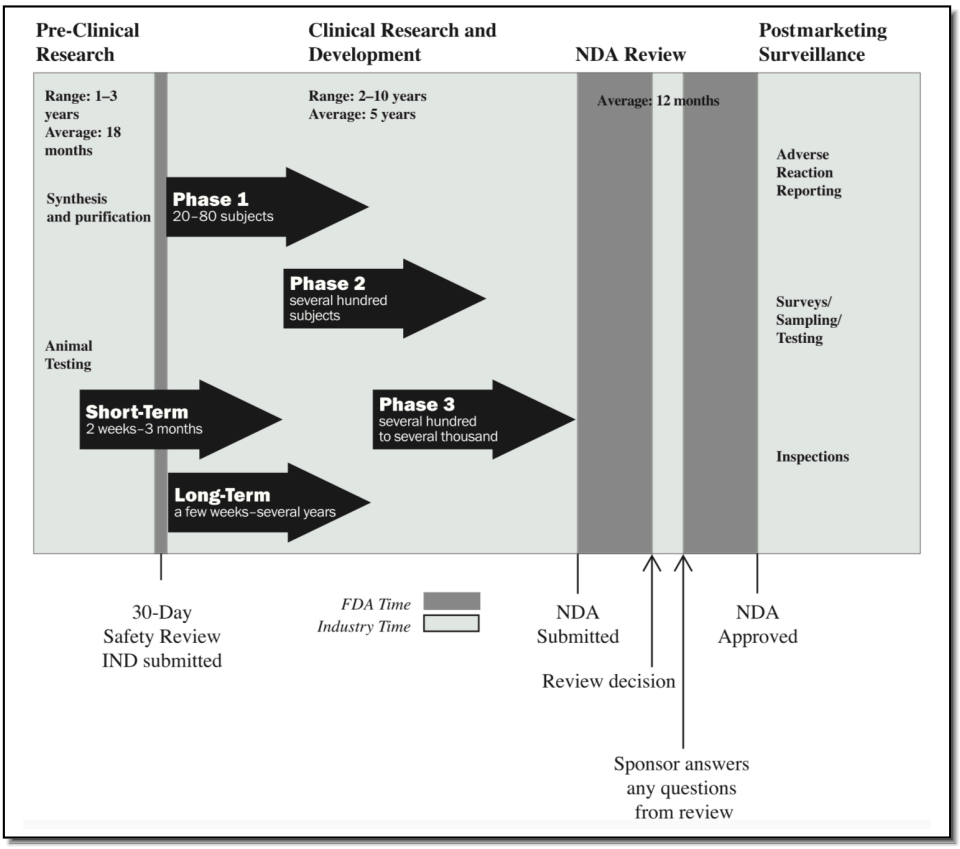


Figure 7: Timeline for the phases of developing a new drug [47]

While human research is needed, because the human follows different pharmacokinetics and pharmacodynamics than animals, the "pre-clinical research" can improve the general safety before the "clinical trial" begins. Studies are often subdivided into different phases [47]:

Phase 0: Exploratory IND studies, limited subjects

Phase 1: Early stage of testing

Phase 2: Preliminary safety and efficacy studies

Phase 3: Expanded large-scale studies

Phase 4: Postmarketing studies

A clinical trial can have different outcomes. It can

1. improve patient outcomes.
2. show no benefit for the patient at all.
3. cause unexpected and potentially dangerous harm for the patient.

All of those outcomes are a potential gain for the trial because the medical knowledge gathered can advance future tests and improve the patient care. [48] The process of study and approval can differ between medical drugs and medical devices. The process of approval can be found in the appendix (appendix C).

Clinical protocols, respectively research protocols are the foundations of every clinical investigation. They describe in detail how a clinical trial with be conducted. [49] It can be said, that the protocol specifies the guidelines for conducting the trial. It contains all the "metadata" of the study, such as the eligibility of the participating patients, the timeframe, the test medications and the tests [50].

To date, clinical protocols, are mostly written as a well-structured text document used as documentation to provide information for the human reader.

However, in the recent years, as protocols have become increasingly complex, they have come to be seen as a vital source of highly formalized information. [51, 39:10]

The Clinical Data Interchange Standards Consortium (CDISC)[6] set out to create the Protocol Representation Model (PRM) back in 2010, with the goal of information management and re-use. [51, 40:39]

David Shoemaker (SVP R&D) and Karen Kesler (AVP Operations) name some particular benefits of PRM. [51, 44:30]

1. to update study summaries automatically
2. transfer of study data into different other systems
3. providing searchable database structures

In the following subchapters, the history of clinical protocols is described in short. Also, the clinical studies and their typical conduct at the university hospital cologne is taken into closer consideration.

[6] A non-profit standards development organization, founded in 1997

2.3.1. Excursion: Evolution of Clinical Research

A short overview of how Clinical Trials evolved over time gives some insight into how things evolved to the complex process established to date.

"The charm of history and its enigmatic lesson consists of the fact that, from age to age, nothing changes and yet everything is completely different" - Aldous Huxley

The first documented event which could be called a clinical trial was in the year 562 BC by the king of Babylon, King Nebuchadnezzar. According to the Bible, specifically the "Book of Daniel", people were ordered to eat meat and drink wine exclusively. As an outcome of that "trial" many people died due to the nourishment ordered. [52] In comparison to of that very early state, clinical studies today are modeled as multiphase trials where medical treatments and prevention strategies can be conducted. [52]

Another remarkable step was the worlds first documented appearance of placebo. According to medical literature, in 1800. This changed clinical trials because it provided a solid point of distinction between the two groups of patients where no established standard treatment is available as reference point. [52] The groups, which patients are set into, are randomized. This is done since the effect of medication could vary based on the persuasion of the patient that the substance will work. To prevent the medical personnel of the study distorting the result by there own bias, even subconsciously, clinical trials are often set up as double-blinded and randomized. This way, not even the medical personnel knows which patients are receiving placebo. [53]

The first attempt of a multi-armed study was in 1753 by the British doctor James Lind who started a trial to cure scurvy. He split twelve sailors into six groups of 2 people each to give them different food supplement. [53] Clinical Trials practice, as known today, goes back to 1946. In 1947, the first International Guidance on the topic of ethics in medical research involving subjects had been formulated in the Nuremberg Code. From that time onward, the World Medical Association in Helsinki has been articulating principles and specific guidelines on how human subjects are to be safeguarded in medical research. The last guideline was published in 2016 (ICH E6 (R2)). [54]

At this point, not all historical events about clinical trials are listed. However, it can be concluded, that the recent years contained many failures when talking about the ethical aspects, as well as some success and the will to improve concepts. Even today, researchers are not always able to prevent all possible harm and research misconducts from the patients. [55]

2.3.2. Clinical Studies at the University Hospital Cologne

The University Hospital of Cologne is one of the leading hospitals in Clinical Research. It hosts the largest clinical trial center in Germany and the comprehensive cancer center has a very strong focus on clinical research. [56] Besides the oncology department hosts the two largest academic research groups in Germany. [11]

This has lead to the fact that a convergence of clinical research and healthcare are dedicated focus. Cliniclalsite.org, a service for trial management on study sites, was developed at the university hospital of cologne and is used by several hospitals in Germany. Also, Cologne is leading an effort in linking the patient records in the EMR to the research record of a study subject. FHIR is the technology of choice and Medical Systems R&D has developed several resources and profiles for this purpose. One essential App developed there is the Subject Management App which is completely modeled on the "ResearchSubjcect" resource.

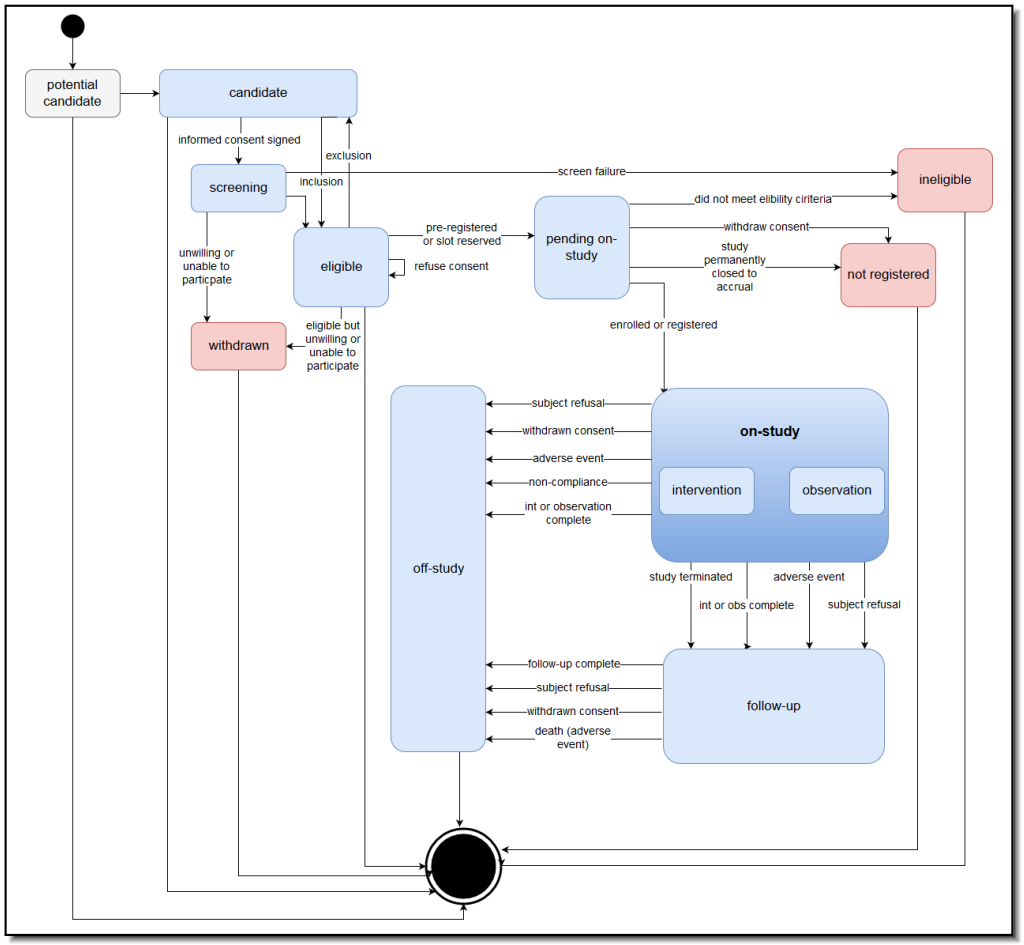


Figure 8: Typical state machine for ResearchSubject [57]

3. Profiling in FHIR

The following chapter aims to provide a general introduction to profiling resources in FHIR. Covering an introduction to FHIR profiling, including an explanation of the hierarchical concept of FHIR resources and how the different resources work together. It is followed by essential techniques and central points to focus on when learning to profile in FHIR.

The company firely provides a profiling academy on their Simplifier-platform. Information used in this chapter refers to the provided methods. [46] Another central source is the FHIR-specification of HL7. [44]

3.1. General information about Profiling

As mentioned before, the FHIR specification describes a set of resources, so-called, base resources (chapter 2.2.3). However, the wide variability of health care data across different institution exacerbates the interoperable communication.

"FHIR aims to standardize functionality that is supported by 80% of systems in use" [58]

As a platform-specification, FHIR is neither capable nor aiming to represent a complete model with the ability of expressing all possible clinical data. It is, however, providing a foundation to build own implementations on. Customizing FHIR resources enables stakeholders to add constraints to a resource, to create a profile and form it to their personal needs.

Since the FHIR standard is designed to build up units of exchange, they need to have a defined behavior and a known identity. [44] Profiles in FHIR can either extend or restrict resources in their usage.

Generally profiles are defined using a "StructureDefinition" resource, as it consists of a statement of rules about how the different elements are used and where extensions are used in the resource. [44]

The conformance layer in FHIR gives details about how resources are used to solve particular use cases. This is done to enable the different applications to exchange data through the fairly loose structure rules of FHIR.

As a new profile entails creating and defining a StructureDefinition, it may include a differential-statement, describing the difference towards the base-resource on which the profile is built on. The full description of the StructureDefinition can be contained inside a SNAPSHOT. However, both of the variations can be present.

In the following table (table 3), the critical resources of the conformance layer are explained.

Resource	Description
ValueSet	A ValueSet defines a set of coded values (take a look at "Using Codes" for more details) that can be used in a particular element.
StructureDefinition	A StructureDefinition is what you build when you build a profile. The StructureDefinition contains rules about how a resource (or type) and its data elements are used in a particular context. A structure definition references value sets for the coded elements in a resource.
CapabilityStatement	A CapabilityStatement is a statement of the kinds of resources and operations provided and/or consumed by a application. The Capability Statement references profiles to describe specific use of resources by the application.
ImplementationGuide	An ImplementationGuide is a document that is published by a domain, institution or vendor that describes how FHIR is adapted to support a certain use case (or set of use cases). An implementation guide is a collection of capability statements, profiles, value sets, and (narrative) documentation describing a set of interoperable applications.

Table 2: Key resources of the conformance layer [58]

3.1.1. Profiling of resources

The general question of why profiling is done is already answered; to help institutions and stakeholders to represent their data model correctly. However Simplifier names more goals [58]:

1. Communicate to humans what is decided or expected
2. Enable automated checking/comparison
3. Support code-generation / runtime discovery
4. Create publishing/exchange eco-system
5. Allow testing conformance

While it is generally possible to work without profiles in FHIR, the solution would be very inconvenient. FHIR profiles enable to check the syntax of a resource by validating the constraints added to the profile. In the best case, the application will do this automatically.

A difference has to be made between layered profiles and derived profiles. The second ones are ”profiles on profiles”, meaning constraints are added on an existing profile, whether the same developer or an external have created it. To understand derived profiles further, the chapter 3.1.2 explains the hierarchy of profiles and how it helps institutions adjusting their resources for particular needs.

3.1.2. Hierarchy of Profiles

FHIR profiles are separated in different layers, also called the hierarchy of profiles. In figure 9, the different level of resources and how compatible those are with the corresponding profiles are shown.

On a higher level ”[...] the profiles are more generic and have a lower volume, while a higher volume of resources will conform to these profiles. At a lower level, the profiles will be more specific and have a higher volume, while there will be fewer resources conforming to these profiles.” [46]

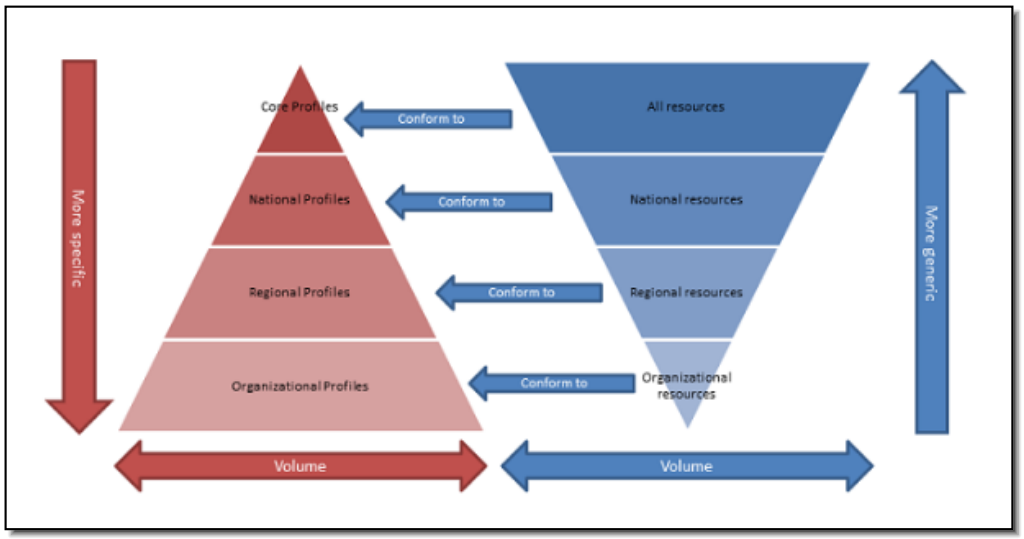


Figure 9: Hierarchy of profiles in FHIR [46]

Starting with the set of all resources, those naturally cover the most significant amount of data. According to the rules of profiling, all resource are compatible and valid in the layer of the ”Core Profiles”. This can be established due to the states (explained in chapter 3.2). Meaning that all FHIR resources have to be compliant to the profiles HL7 is providing in the standard.

Going down the levels, the ”National resources” can be validated against the profiles on a national level, but not necessarily against the core profiles. Giving a concrete example at this point, not all nations need the same fields and clinical information in their resources.

Some might need different fields, need to restrict profiles, force them to contain a particular field, or extend them by details as in this specific example.

The patient base profile of Germany, for example, contains an extension in the form of an identifier named ”VersichertenID_GKV”. This relegates to the health insurance and the unique identifier of the patient and is a unique identifier, not included in the FHIR base profile of the patient (appendix D.1).

The Netherlands, on the other hand, don’t need this precise identifier; however, they include an extension named ”preferredPharmacy” to refer to the patient’s preferred pharmacy (appendix D.3).

Both nations have developed their base profile of the patient resource, based on the code profile, provided by HL7 FHIR (figure 10).

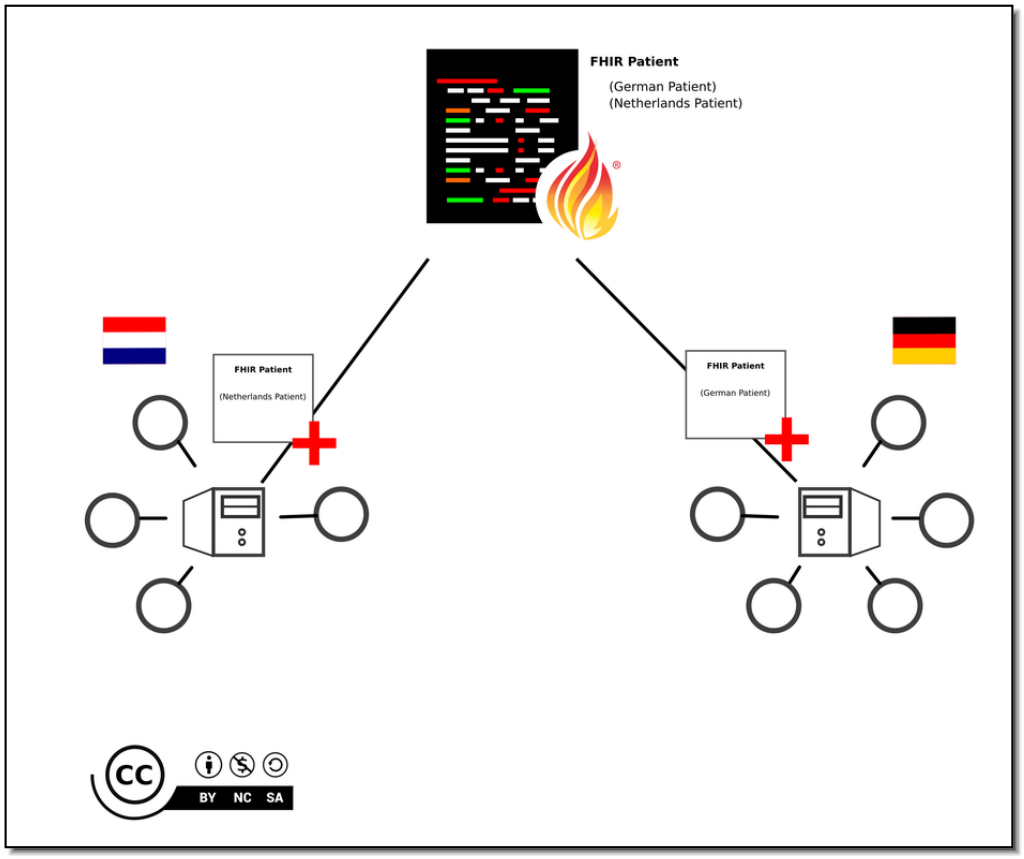


Figure 10: Example of national Profiles in FHIR [42]

Going on with the profiles of the different nations, regions can define their derived profiles based on a higher layered profile. They can choose to use the national profiles, as well as the core profiles for some reason.

When an organization or an institution, like in the concrete use case of this thesis the University Hospital of Cologne, need more specific information, they can adopt an existing profile in the hierarchy and adjust their changes to match the internal workflow and stay interoperable to a certain level on cross-organizational communication.

The different layers of profiles are not limited to the four displayed in figure 9. If for some reason additional profiles on a separate layer are needed, FHIR doesn't have any rules about restricting the number of profiles or layers.

However, the scaling of profiles, down to the organizational level as an example, is limited up to a certain point. The different techniques and limitations can be found in chapter 3.2.

3.2. Limits and Scope of Profiling

An important aspect when discussing the limits and the scope of profiling is to determine what can be profiled. As stated in the ProfilingAcademy, profiling usually starts with a core resource of FHIR, for example, the Patient resource.

A typical example would be, to use the element name or the resource and extend the minimum cardinality to 1 using a profile. By this process, the name becomes obligatory. The birthplace, as a second example, can be customized to the maximum cardinality of 0. This would remove that element from the profiled resource.

Giving these examples, it has to be mentioned that the profiling of cardinalities in FHIR is limited too. A profile can restrict the cardinality, but only within the limits of the base structure. The following table (table 3) shows what changes of the cardinalities are allowed and which ones are out of bounds.

derived/base	0..0	0..1	0..n	1..1	1..n
0..1	yes	yes	no	yes	no
0..*	yes	yes	yes	yes	yes
1..1	no	no	no	yes	no
1..*	no	no	no	yes	yes

Table 3: Allowed changes in cardinality using profiling [44]

Besides changing the existing elements, new ones can be added too. As an example, the hair color of the patient could be relevant. It's also important to mention that codes and valueSets can be modified. Talking about the example of the patient resource, the own "haircolor"-extension could be limited to a particular list of values, or it could refer to a coding-system like SNOMED CT (explained earlier in this thesis, take a look at chapter 2.1).

In the following sections, different elements and parts of the profiling-process are explained further. At this point, not all aspects of profiling can be described in detail. The focus is therefore set onto building up a general understanding of the different elements and providing the base for a further understanding of this thesis. The technical aspects and unique toolings are not explained in detail and cannot be seen as part of the following description.

3.2.1. Extensions

Up to this point, core resources have been mentioned a few times. Because it would be hardly possible for FHIR to incorporate all stringent requirements, the specification is designed to allow the previously mentioned additional implementations; the so-called extensions. The ProfilingAcademy writes that "Extensions are a way to extend an element or resource to include additional elements not present in the original, e.g., adding a birthplace in addition to the date on the Patient resource." [59]

For clinical safety, FHIR has included an *"isModifier"*-Flag. This is used, when a resource is changed significantly in its conceptual understanding. In typical cases, the system tries to process every resource, even if it doesn't understand a specific extension. The *"isModifier"*-Flag signals the system, that processing without understanding the full context is not safe.

To use extended resources in the daily workflow and sending them to different systems, it has to be made sure that the resources are published (for example on Simplifier.net)

Worthy to note at this point is the "Extension Definition", which defines an URL to identify the extension. Further, it describes the context where the extension can be used, meaning a single extension has to be defined once and can be reused in different profiles.

3.2.2. Slicing

Adding a specific constraint to an element can be to strict, in case that the constraint shouldn't apply to the whole element. Slicing is the logical option to create different parts of an element, named slices, which can contain constraints that are contradictory to each other.

To help the system identify the different slices, a discriminator is used. It should allow systems to determine which slices belong to which section. Initially slicing an element, the discriminator has to be assigned. To do this, the path and the type need to be determined.

The ProfilingAcademy states that FHIR defines five different types [60]:
value - "The slices have different values in the nominated element"
exists - "The slices are differentiated by the presence or absence of the nominated element"
pattern - "The slices have different values in the nominated element, as determined by testing them against the applicable ElementDefinition.pattern[x]"
type - "The slices are differentiated by type of the nominated element to a specified profile"
profile - "The slices are differentiated by conformance of the nominated element to a specified profile"

By the time an element is sliced, the creator can decide whether or not he/she wants to allow additional content added to the different slices. FHIR specifies three different rules, about how to define this (table 4).

An example, mentioned in the Simplifier Profiling Academy is that the Netherlands have different ways how to identify practitioners (UZI number, AGB code, BIG code) [46]. In case that UZI number and AGB code are slices, and the rule is defined "open", the BIG code can be added. When the rule is defined as "close", the BIG code cannot be added. Lastly with the rule allowing "open at end", the BIG code can be added, but just at the end of the identifier-list. [60]

Code	Definition
closed	No additional content is allowed other than that described by the slices in this profile.
open	Additional content is allowed anywhere in the list.
openAtEnd	Additional content is allowed, but only at the end of the list. Note that using this requires that the slices be ordered, with makes it hard to share uses. This should only be done when absolutely required.

Table 4: Rules about the usage of slicing [60]

A small example of HL7 how slicing can look like is visualized. Here, shown in figure 11, the "component" element contains a nested code and a value attribute. Profiling a "Blood Pressure Profile", as a common example, the component is sliced into two different slices. One for "Systolic" and one for "Diastolic" pressure. As seen in the picture, the different values also got different constraints for valueSets in the form of "CodeableConcepts" to use.

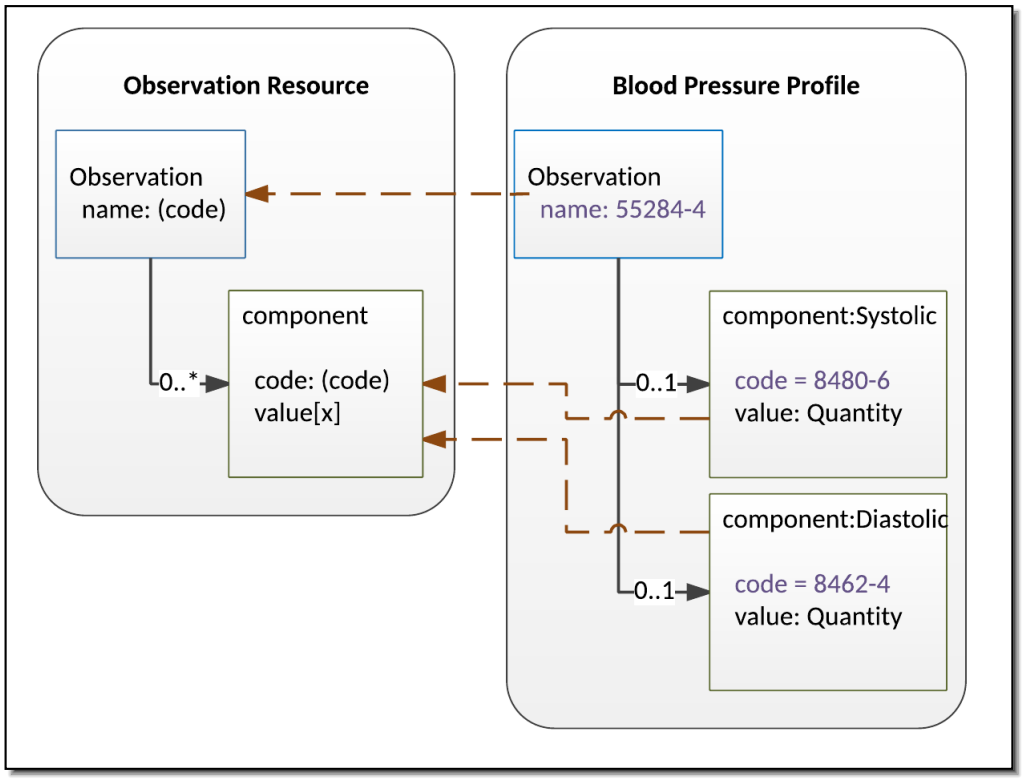


Figure 11: Example of the slicing process on the Observation resource [44]

Another example of a sliced resource, in the form of a MedicationStatement in XML-format, can be found in the appendix (appendix E).

3.2.3. Terminology

Terminology is generally about the codes in the available data. A few different FHIR resources cover it. Figure 12 is showing those resources and their relations.

The CodeSystem is defining a set of concepts. These codes can be used to describe the inventory and values of specific clinical content. Further, the ValueSet defines a selection of codes to be used in particular content. Concerning the CodeSystem, the ValueSet selects codes from one or more different sources.

Different data types can describe the data of CodeSystems in Coded Data Types.

1. **Code** - The list of codes is fixed. A common example is the gender
2. **Coding** - ”contains elements to capture the system, its version, the value of the code itself and a textual representation” [46]
3. **CodeableConcept** - Contains 1-n Codings, as well as an optional textual representation

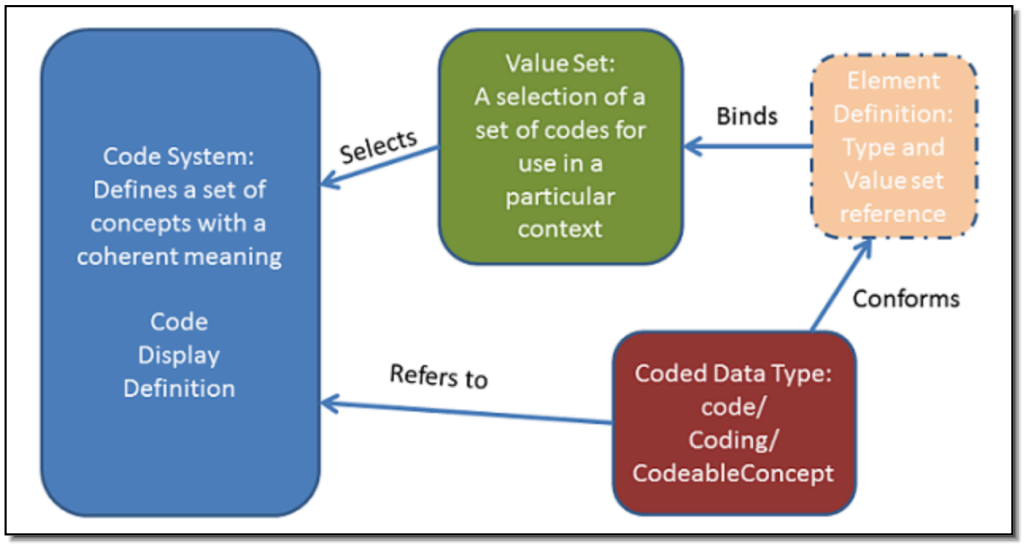


Figure 12: Concept map of terminologies in FHIR [46]

When used in profiling, the ”CodeableConcept” is usually the safest choice, since it includes the Coding which enables the profile to be reusable.

Lastly, the ”Elemental Definition” defines a particular element in a resource or an extension. Taken the name of a patient as an example, it has different properties like the cardinality or the data type. The elemental definition is further defining the data type and the ValueSet for the individual element.

The Terminology, in the context of profiling, refers mainly to the ValueSet and the CodingSystem resources. What should be known about terminology is, that a field has a ”strength of the binding” to a particular ValueSet.

Binding strength	Meaning	How you can profile this
Required	You can only select codes from this valueset and no other	You can remove codes from the valueset but you cannot add any new codes
Extensible	You must select code from this valueset, but you can use other codes if the valueset doesn't have a matching code	You can add and remove codes from the valueset but don't duplicate or replace existing ones
Preferred	You should select codes from the valueset, but it's not strictly necessary	You don't have to use these codes, but it's recommended that you do
Example	This is just an example of codes you could use	You should set this to a valueset of your own or at least strengthen the binding

Table 5: Strength of the binding in ValueSets [46]

3.2.4. Profiling Tools

FHIR has several tools available to help developers and consultants while creating and customizing profiles. Besides the basics of building and designing a profile, it can also come into the discussion, if a profile about an individual use case has already been designed. Several public pages are a good start to search for potential public profiles, these include, but are not limited to:

1. **FHIR Registry**[7] "[...] is a central point to search for published FHIR Resources: profiles, extensions, terminology-related and all others created for FHIR STU3 in International, National, Institute or Regional projects on simplifier.net" [61]
2. **Simplifier**[8] "[...] is a FHIR registry. You can find FHIR profiles, view and learn about them and other FHIR conformance resources, like extensions, valuesets, and more. Simplifier is the ideal place to learn about the relationship between different profiles." [62]
3. **FHIR Extensibility registry**[9] is the official registry by HL7. Just like the other options, this registry contains a collection of customized "StructureDefinitions". It is particularly referencing towards http://hl7.org/fhir/registry as another registry.

The philosophy of FHIR is to be public and free-of-charge. To support this and the common sense of interoperability, it is crucial to keep profiles as close and conform to national and regional profiles as possible. So when profiles are published, they can be used by other companies and stakeholders without much effort.

To support this, personal solutions and ideas should be published for the community to find and extend them for personal and collaboration needs.

To help developers understanding profiles and make working with them easier, some naming conventions are to be followed. According to the Simplifier Profiling Academy [63], those rules include:

1. UpperCamelCase for resources
2. lowerCamelCase for elements and slices (chapter 3.2.2
3. lowercase for extensions, using the following format: [context]-[name]
4. Consider to include the resource type of the customized resource in the name of your profile

[7] https://registry.fhir.org
[8] https://simplifier.net
[9] http://hl7.org/fhir/STU3/

The narrative in FHIR represents a textual description of what the resource/profile is used for. To support this, a short description of the usage, or at least if it is an extension or a profile, should be included.

Different projects, however, can have a different scope. Depending on that, a different attempt at profiling can be used. The two approaches to be discussed is the close and the open modeling. On the one hand, an open model is generally more generic, due to a lower amount of constraints defined. Regional projects are advised to use this model because it enables generally higher flexibility for downstream projects. Due to the more generic kind of modeling, the profiles can be reused easier and with less effort.

The closed modeling approach limits the profile by adding more constraints and reducing the possible data the profile can contain to the minimum necessary.

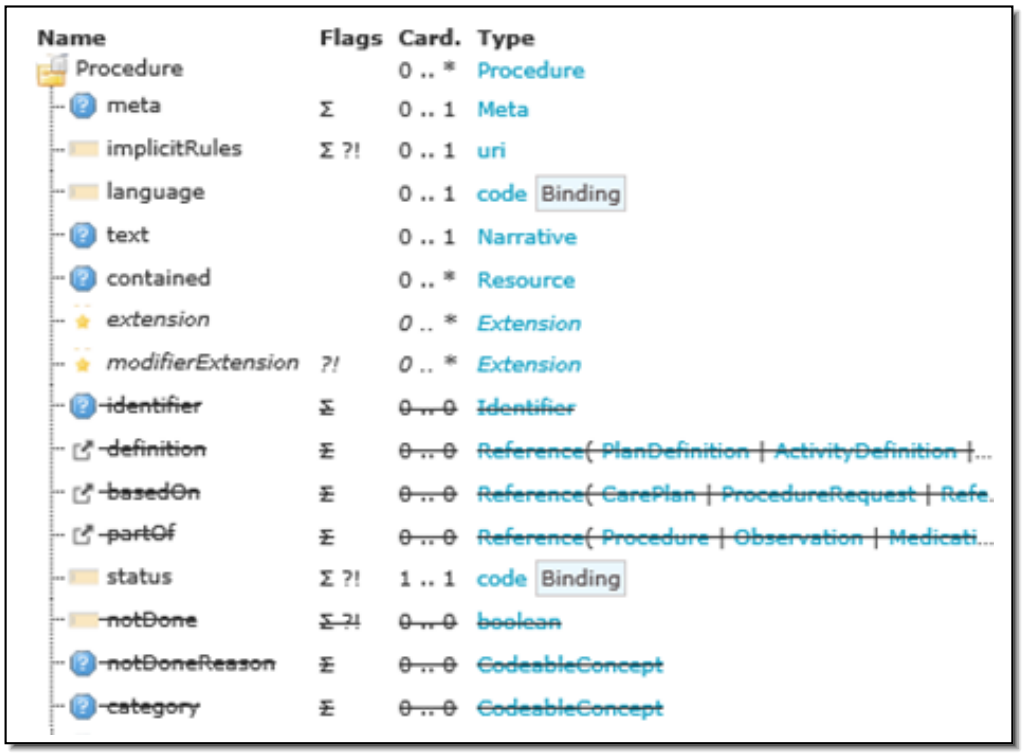


Figure 13: Profiling using the closed model approach [63]

Downstream projects should mostly go the way of making a closed modeling approach. This way the required data can be easily circumscribed. These profiles are modeled by constraining the maximum cardinality of unused fields to 0. This can be done by slicing the elements (chapter 3.2.2) and setting constraints on the slide, limiting the cardinality.

A huge benefit of the closed modeling is that application with a graphical user interface can represent the received data without having to use custom filters to reduce the data displayed to the relevant fields.

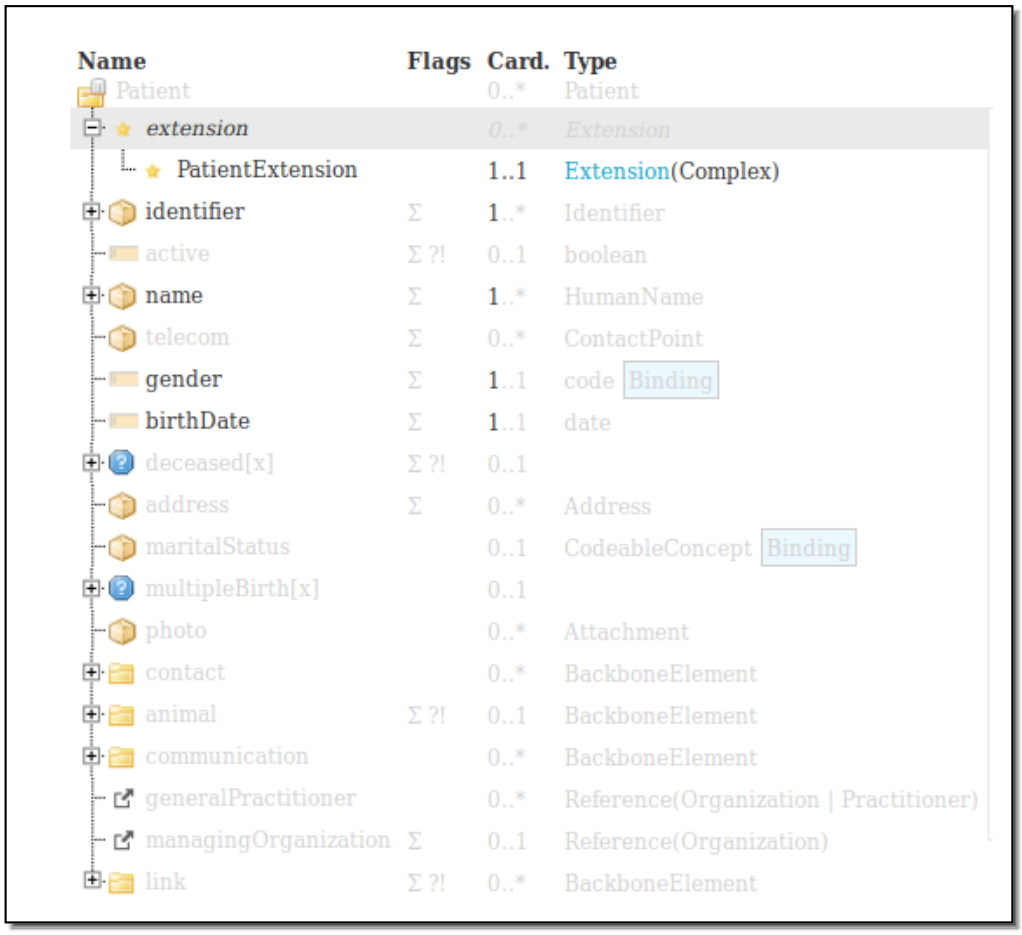


Figure 14: Profiling using the open model approach [63]

Designing a profile according to the open modeling approach doesn't limit the cardinality, allowing the end-user to fill in the necessary data, even though it is not explicitly used to the defined use case.

Though this approach is increasing the amount of data that needs to be covered, some of the information transferred might not be processed by the application and are filtered out.

Still, creating a derived profile of an open modeling approach leaves the designer with more possibilities to scope the profile to their personal needs. Customizing a closed modeling approach, like shown in figure 13, the developer is not able to re-enable for example the "notDone"-attribute, since the cardinality was set to 0..0 before (for possible cardinalities, take a look at chapter 3.2).

The following table shows the pros and cons of both different modeling techniques.

	Open modeling	Closed modeling
Pros	Forward compatibility	No need to support all elements
	Focus on what must be supported	More specific models
	More generic data fit	Smaller, straightforward models
		More implementer feedback
Cons	More elements have to be supported	More versions of models
	Larger, vaguer models	Only backwards compatibility
	Less implementer feedback	New elements require new version

Table 6: Advantages and disadvantages of different modeling (adapted from [46])

The table doesn't claim to be entirely exhaustive but to name the most important aspects. Different projects have to choose individually if open or closed modeling is a better choice for their specific use case.

4. Clinical Studies

Clinical investigations always start with the development of clinical protocols. The protocol, in the form of a document, describes how clinical trials will be conducted - including objective(s), design, methodology, statistical considerations and the organization of the trial. It also ensures measures to safeguard the safety of the participants and the integrity of the collected data.

4.1. Setup of a Clinical Trial

The information on the general setup of a clinical trial is generally also found at high-level synopses of the trial.

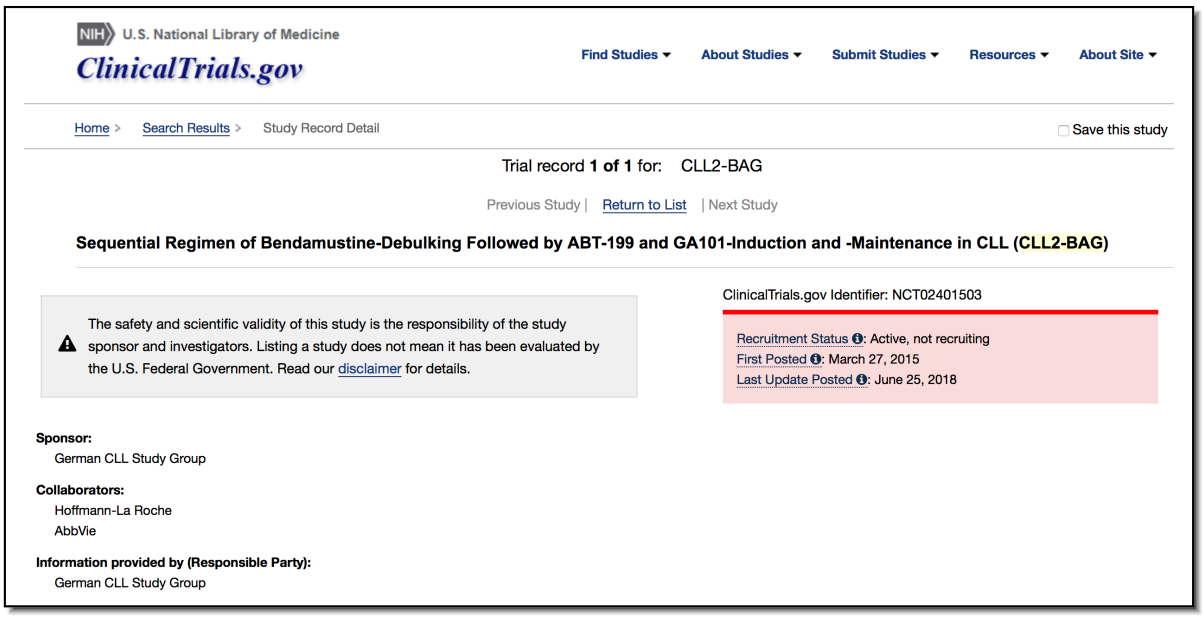


Figure 15: example of a study on clinicaltrials.gov [64]

The public webpage "clinicaltrials.gov" provides the opportunity to view different public trials and get to know the various aspects further. Central aspects of conducting clinical trials are:

- Objectives/Purpose
- Study Design
- Selection and Exclusion of Subjects

A distinction has to made between clinical trials and observational studies. In the following work, clinical trials are set into focus.

4.2. Clinical Trial Protocol

A research protocol describes the background, rationale, objectives, design, methodology, statistical considerations, and organization of a clinical research project. Besides the main setup of items listed above, a protocol should include the following topics (based on ICH Good Clinical Practice guidelines) [65]:

- Treatment of Subjects
- Assessment of Efficacy
- Assessment of Safety
- Adverse Events
- Rules for deciding when to discontinue the Study
- Statistics
- Quality Control and Assurance
- Ethics
- Data handling
- Project Timetable/Flowchart
- References
- Supplements/Appendices

The most complex aspects of this list are the "Treatment of Subjects", "Assessment of Efficacy" and "Assessment of Safety". They entail describing procedures, which are scheduled in so-called "visits". They have to be performed in a very rigid timeframe.

We will here focus on two different and equally important aspects. The first is the "Schedule of Activites" (chapter 4.2.1) and second is the "Dosing and Administration" (chapter 4.2.2).

4.2.1. Schedule of Activities

The procedures to be accomplished at each study visit have to be captured by the schedule of activities. This also includes, among other aspects, any tests for eligibility, participant randomization or stratification and decisions on study intervention discontinuation. Different procedures, contributing to the participant's eligibility, should be annotated to distinguish between other routine procedures. Study objectives and endpoints need to be annotated too.

Procedures which are not directly related to the trial need to be captured sparingly and with consideration, as they can possibly add unnecessary complexity and distract from recruitment.

To determine the appropriate windows - which should be stated for all visits - considering the feasibility and relevance of the visit time points to study endpoints is essential.

4.2.2. Dosing and Administration

This description stipulates the procedures for selecting a participant's dose of study intervention and control product. With a focus on drugs, that includes the duration (e.g., the length of time) as well as the timing of the doses (e.g., time of day and interval). Also, the planned route of administration (e.g., oral or intravenous) must be taken into account.

In the protocol, this part states the starting dose and schedule during the study intervention and control product. It also includes the maximum and minimum duration for the participants who continue to stay in the study.

The protocol will, if applicable, describe the dose escalation schema and dose regimen. It will further state any minimum period required before a participants dose might be raised to a higher dose or dose range.

For this to be applicable, the protocol should further state the conditions necessary to change the particular doses of a patient. In particular with regard to toxic or other warning indicators.

It will address dose modifications, especially for specific abnormal laboratory values of concern or other adverse events (AEs), which are known to be associated with the planned study intervention.

The protocol must provide criteria, used to determine dose escalations. It also has to state the dose-limiting effects, which are anticipated, explicitly.

Positive responses to the intervention by participants have to be mentioned in the protocol too. It needs to specify whether study intervention administration would progress to still higher doses. If appropriate, provide a dose de-escalation schema with intervention modifications.

Specific instructions to participants of the study, about when or how to prepare and take the dose(s) need to be described. It has to include, how delayed or missed doses should be handled. Specific instructions and safety precautions for the administration of the study intervention have to be included too.

5. Approach of mapping FHIR Profiles to Research Protocols

In 2015, Hugo Leroux, Alejandro Metke-Jimenez, and Michael John Lawley approached building a mapping between CDISC ODM and FHIR [66]. While this approach is neither entirely obsolete, or the only possible solution of mapping the data, it provides an overview of how a reasonable mapping approach could have looked like.

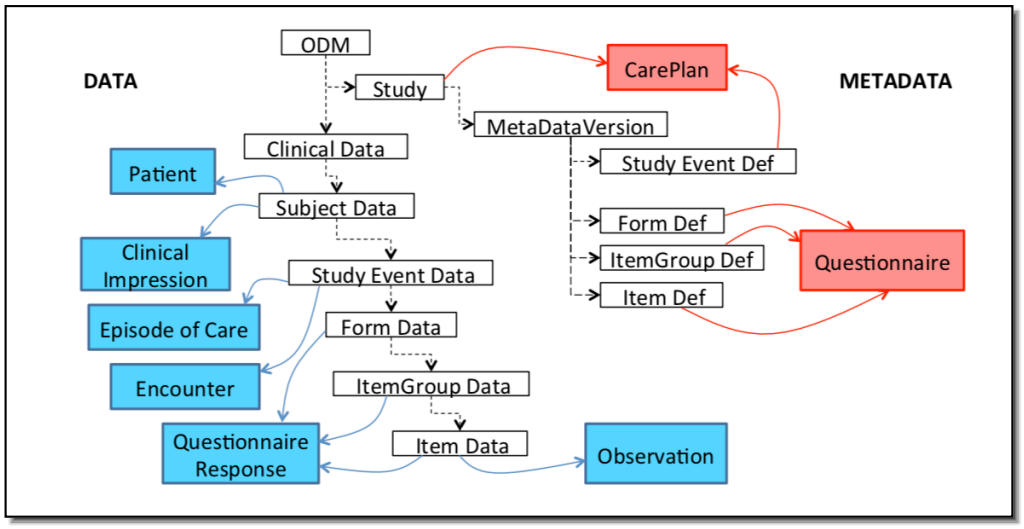


Figure 16: Approach for mapping CDISC ODM Resources to FHIR [66]

Since this model was created back in 2015, some of the resources can be mapped to a better and more efficient way nowadays. Also, the shown model is not comprehensive in the way it is representing resources. FHIR generally offers the "ResearchStudy" resource, which has the maturity level 0. This means that the resource was published in the current release. The following approach is, therefore, trying to build an initial mapping of clinical trials, especially the clinical protocols, based around the "ResearchStudy" resource (chapter 5.1.1).

In general, this chapter discusses a more up to date approach for mapping FHIR resources to research protocols. Due to the limited time of this thesis and the complexity of the data, not the whole process of storing clinical trial protocols can be discussed.

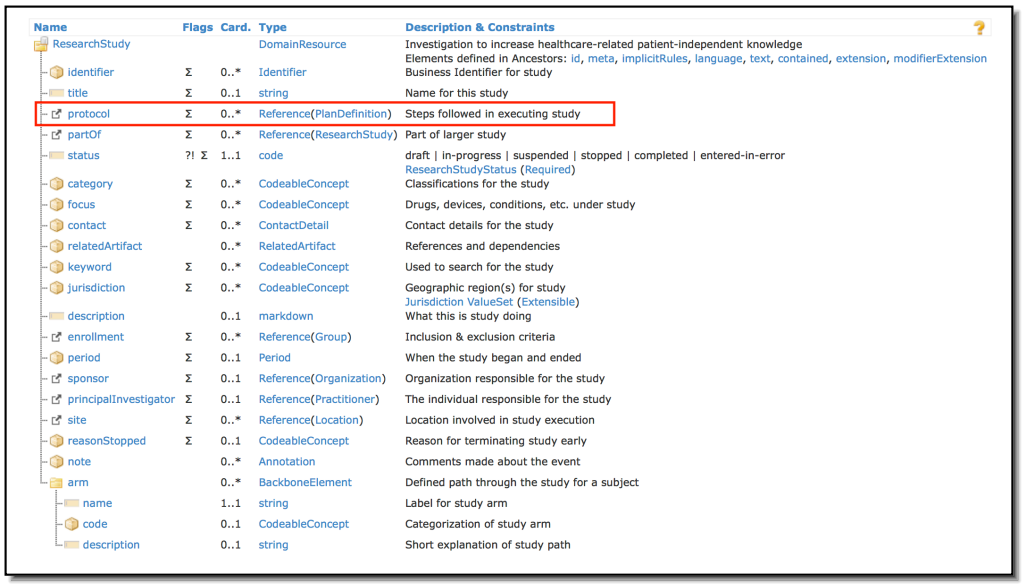
5.1. Representing Clinical Trials as FHIR Resources

In the following subchapters, the detailed approach of representing clinical trials as FHIR resources is discussed. We start with an analysis of the different resources FHIR is providing to represent the study. We chain the resources together as much as possible to build a coherent construct.

We follow with a profiling solution of the problem and an analysis about how the answer can be integrated into existing resources, as well as a proof of concept by creating a resource chain of the most essential resources.

5.1.1. General representation of Clinical Studies in FHIR Profiles

FHIR does support the concept of clinical trials in the latest release[10] by using the resource "ResearchStudy" (figure 17). HL7 defines the scope and usage with "[...]developing RCRIM[11] standards to improve or enhance information management during clinical research and regulatory evaluation of the safety, efficacy, and quality of therapeutic products and procedures worldwide." [67]



Name	Flags	Card.	Type	Description & Constraints
ResearchStudy			DomainResource	Investigation to increase healthcare-related patient-independent knowledge Elements defined in Ancestors: id, meta, implicitRules, language, text, contained, extension, modifierExtension
identifier	Σ	0..*	Identifier	Business Identifier for study
title	Σ	0..1	string	Name for this study
protocol	Σ	0..*	Reference(PlanDefinition)	Steps followed in executing study
partOf	Σ	0..*	Reference(ResearchStudy)	Part of larger study
status	?! Σ	1..1	code	draft | in-progress | suspended | stopped | completed | entered-in-error ResearchStudyStatus (Required)
category	Σ	0..*	CodeableConcept	Classifications for the study
focus	Σ	0..*	CodeableConcept	Drugs, devices, conditions, etc. under study
contact	Σ	0..*	ContactDetail	Contact details for the study
relatedArtifact		0..*	RelatedArtifact	References and dependencies
keyword	Σ	0..*	CodeableConcept	Used to search for the study
jurisdiction	Σ	0..*	CodeableConcept	Geographic region(s) for study Jurisdiction ValueSet (Extensible)
description		0..1	markdown	What this is study doing
enrollment	Σ	0..*	Reference(Group)	Inclusion & exclusion criteria
period	Σ	0..1	Period	When the study began and ended
sponsor	Σ	0..1	Reference(Organization)	Organization responsible for the study
principalInvestigator	Σ	0..1	Reference(Practitioner)	The individual responsible for the study
site	Σ	0..*	Reference(Location)	Location involved in study execution
reasonStopped	Σ	0..1	CodeableConcept	Reason for terminating study early
note		0..*	Annotation	Comments made about the event
arm		0..*	BackboneElement	Defined path through the study for a subject
name		1..1	string	Label for study arm
code		0..1	CodeableConcept	Categorization of study arm
description		0..1	string	Short explanation of study path

Figure 17: ResourceStudy Resource [67]

Besides some general information, such as the title of the study or the current status, FHIR also provides the field "arm" to support multi-armed studies (information about multi-armed studies are found in chapter 2.3.1) The "protocol" field allows a reference to a "PlanDefinition" resource. Standing at the maturity level 2 means, that the resource has already been exchanged "between at least three independently developed systems leveraging at least 80% of the core data elements" [68]

[10]The currently latest release of FHIR is STU3, released at the 19th April 2017
[11]Regulated Clinical Research Information Management

As to the ”PlanDefinition” resource, it can be described as a pre-defined set of actions, however still be flexible to represent a vast area of workflows. ”PlanDefinitions” can contain a list of actionDefinitions, where particular actions describe activities to be performed.

Figure 18 shows the reference relationship between ”PlanDefinition” and ”ActivityDefinition” resources.

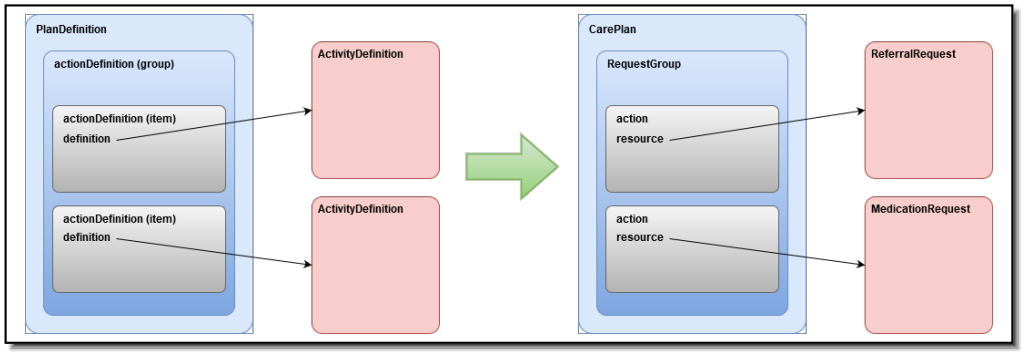


Figure 18: Relationship between PlanDefinition and ActivityDefinition [69]

For this approach the relevant fields in the ”PlanDefinition” resource are ”action” with a cardinality of 0..* (from 0 to many) and the subfield ”definition” with a cardinality of 0..1 (exactly 0 or 1 time). These fields are shown in figure 19 and figure 20.

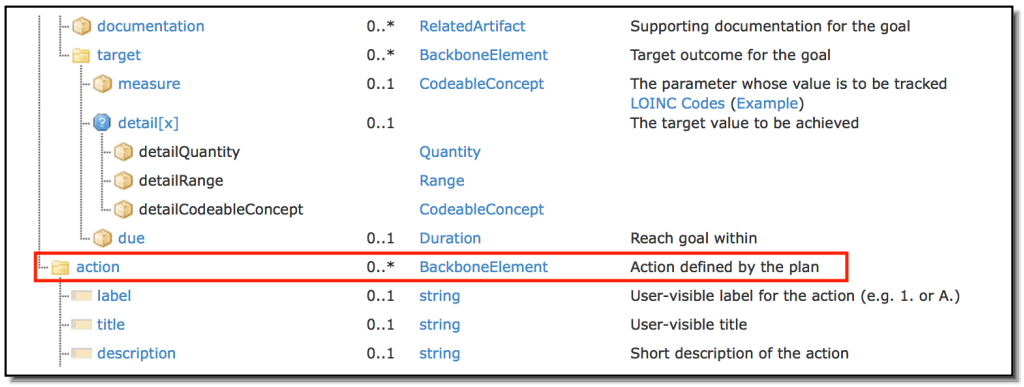


Figure 19: ActionDefinition in the PlanDefinition resource [69]

An action is a ”BackboneElement”, meaning it is defined as part of a resource definition (in this case ”PlanDefinition”). In general ”BackboneElements” can be described as elements which are only internally available inside a resource. With the knowledge of a software engineer, these are comparable to anonymous classes in object-oriented programming. According to the definition of the standard, Data Type elements are not using it generally. [70]

As mentioned before, the focus is mainly set into the definition (shown in figure 20), which is, if stated, a reference onto an ”ActivityDefinition” or another ”PlanDefinition”

resource.

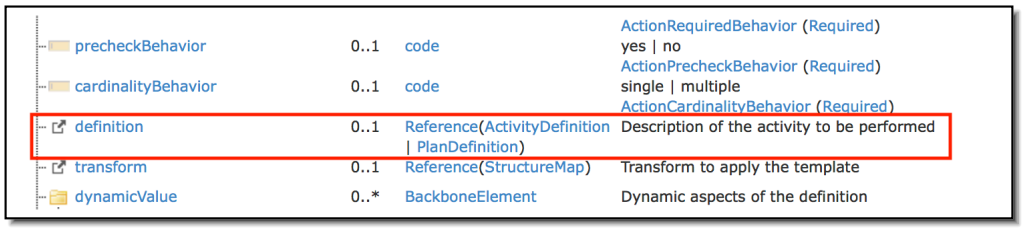


Figure 20: ActivityDefinition in the ActionDefinition of the PlanDefinition resource [69]

As the name indicates, the "ActivityDefinition" describes an activity to be performed. HL7 states that the "ActionDefinition" itself doesn't indicate the actual intent to carry out a particular action but can be seen more like a reusable template used to construct specific request resources like "ProcedureRequest"[12] or "MedicationRequest"[13].

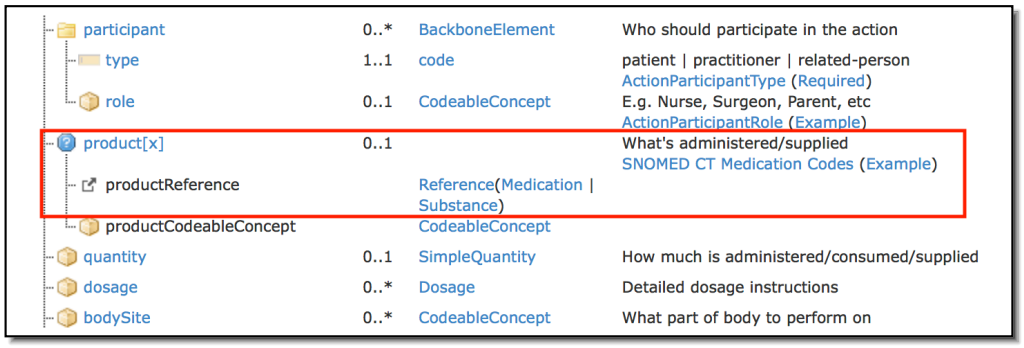


Figure 21: Reference to Medication in the ActivityDefinition resource [71]

As shown in figure 21, the "ActivityDefinition" resource, however, contains the field "product[x]" which has the subfield "productReference". Through this, "Medication" and "Substance" resources can be referenced.

Though this List of resources is not exhaustive, it provides an idea of how FHIR handles the representation of a clinical trial so far. Summarized, the reference flow of the resources from the definition of the study to the medication can therefore be described as:

ResourceStudy → *PlanDefinition* → *ActionDefinition* → *ActivityDefinition* → *Medication*

Important to note at this point is, that cardinalities of "ResourceStudy" to "PlanDefinition" and from "PlanDefinition" to "ActionDefinition" are 0..*, meaning it doesn't have to appear but can also be instantiated multiple times. The references to ActivityDefinition and Medication are also optional, but with a cardinality of 0..1, meaning they can appear one time at maximum.

[12]https://www.hl7.org/fhir/procedurerequest.html
[13]https://www.hl7.org/fhir/medicationrequest.html

5.1.2. Problems about the current representation

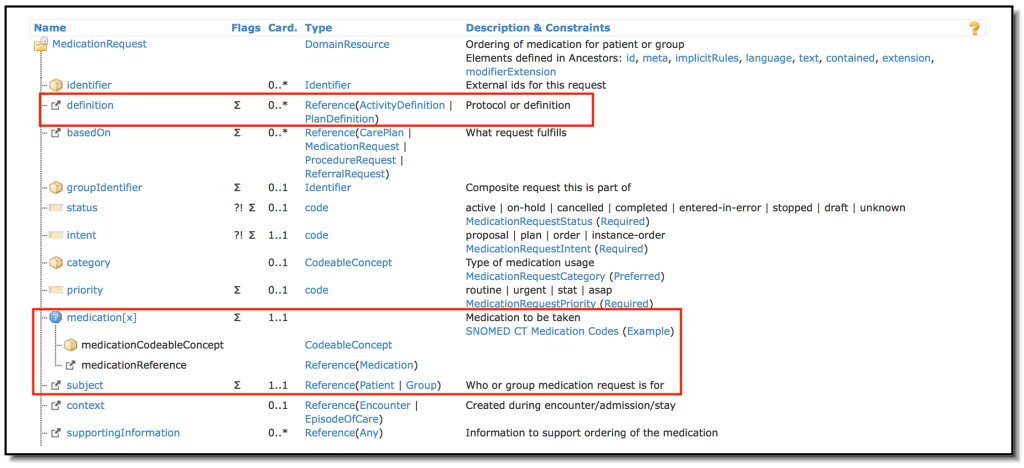
Even though the resources and references FHIR provides already cover a vast area of the aspects needed for clinical trials, not every use case can be easily depicted; without some adjustments at least.

The logical approach for planning a clinical trial would be, the "ResearchStudy" resource providing the general representation. It can refer to "PlanDefinitions", which can themself relate to multiple "ActivityDefinitions".

There are several issues to point out here: The "Medication", related in an "ActivityDefinition" doesn't represent a real dose of medication for a patient to take, but only a representation of the drug itself.

While "ActivityDefinition" (figure 21) can describe the doses of medication on an abstract level, as is needed for the planning clinical trials, a representation of the substances (medication), as well as logging - whether the drug was taken - is needed on the level of an individual patient.

The "MedicationRequest" resource (figure 22) is able to visualize the medication to be taken by a specific patient.



Name	Flags	Card.	Type	Description & Constraints
MedicationRequest			DomainResource	Ordering of medication for patient or group Elements defined in Ancestors: id, meta, implicitRules, language, text, contained, extension, modifierExtension
identifier		0..*	Identifier	External ids for this request
definition	Σ	0..*	Reference(ActivityDefinition | PlanDefinition)	Protocol or definition
basedOn	Σ	0..*	Reference(CarePlan | MedicationRequest | ProcedureRequest | ReferralRequest)	What request fulfills
groupIdentifier	Σ	0..1	Identifier	Composite request this is part of
status	?! Σ	0..1	code	active | on-hold | cancelled | completed | entered-in-error | stopped | draft | unknown MedicationRequestStatus (Required)
intent	?! Σ	1..1	code	proposal | plan | order | instance-order MedicationRequestIntent (Required)
category		0..1	CodeableConcept	Type of medication usage MedicationRequestCategory (Preferred)
priority	Σ	0..1	code	routine | urgent | stat | asap MedicationRequestPriority (Required)
medication[x]	Σ	1..1		Medication to be taken SNOMED CT Medication Codes (Example)
medicationCodeableConcept			CodeableConcept	
medicationReference			Reference(Medication)	
subject	Σ	1..1	Reference(Patient | Group)	Who or group medication request is for
context		0..1	Reference(Encounter | EpisodeOfCare)	Created during encounter/admission/stay
supportingInformation		0..*	Reference(Any)	Information to support ordering of the medication

Figure 22: Representation of the MedicationRequest resource [72]

As shown in the picture, the field "MedicationRequest.definition" allows a reference to an "ActivityDefinition". Contextually this describes the process of conducting a particular record out of the abstract template for an individual patient.

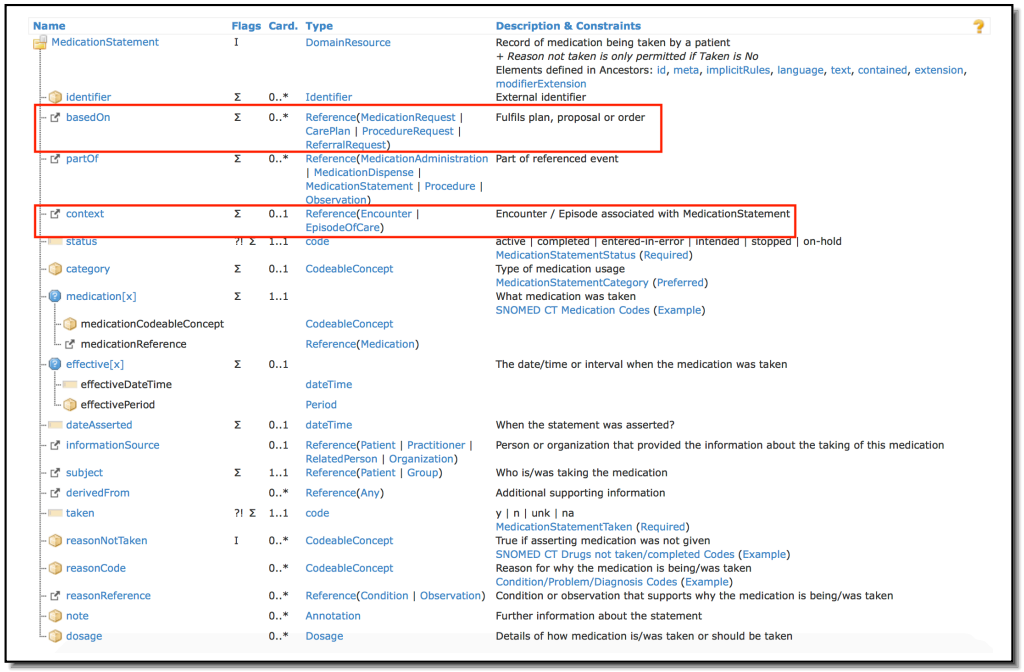
Since the particular scenario requires a concrete "Medication" as well as a subject to receive the medication, both are referenced in "MedicationRequest.medication[x]", allowing a reference to a "Medication", and "MedicationRequest.subject" respectively. "MedicationRequest.subject" in turn references towards a "Patient" or a "Group".

Based on the request, figure 23 shows the state of affairs of the patient. It can be compared with a nominal vs. actual comparison - i.e., planned vs. given dose.

The ”MedicationStatement” resource is, for example, stating elements like the date where the statement was asserted and must have the declaration included as to whether the patient has taken the drug. It also contains multiple references, which are necessary to close the chain of the resources used by a study and fit into its place correctly.

On the one hand, ”MedicationStatement.basedOn” can refer to one of the previously discussed ”MedicationRequests”, allowing to compare between the planned medication of the particular patient and the taken doses.

The field ”MedicationStatment.context” on the other hand is referencing towards an ”Encounter” or an ”EpisodeOfCare”, describing the visit.



Name	Flags	Card.	Type	Description & Constraints
MedicationStatement	I		DomainResource	Record of medication being taken by a patient *+ Reason not taken is only permitted if Taken is No* Elements defined in Ancestors: id, meta, implicitRules, language, text, contained, extension, modifierExtension
identifier	Σ	0..*	Identifier	External identifier
basedOn	Σ	0..*	Reference(MedicationRequest | CarePlan | ProcedureRequest | ReferralRequest)	Fulfils plan, proposal or order
partOf	Σ	0..*	Reference(MedicationAdministration | MedicationDispense | MedicationStatement | Procedure | Observation)	Part of referenced event
context	Σ	0..1	Reference(Encounter | EpisodeOfCare)	Encounter / Episode associated with MedicationStatement
status	?! Σ	1..1	code	active | completed | entered-in-error | intended | stopped | on-hold MedicationStatementStatus (Required)
category	Σ	0..1	CodeableConcept	Type of medication usage MedicationStatementCategory (Preferred)
medication[x]	Σ	1..1		What medication was taken SNOMED CT Medication Codes (Example)
medicationCodeableConcept			CodeableConcept	
medicationReference			Reference(Medication)	
effective[x]	Σ	0..1		The date/time or interval when the medication was taken
effectiveDateTime			dateTime	
effectivePeriod			Period	
dateAsserted	Σ	0..1	dateTime	When the statement was asserted?
informationSource		0..1	Reference(Patient | Practitioner | RelatedPerson | Organization)	Person or organization that provided the information about the taking of this medication
subject	Σ	1..1	Reference(Patient | Group)	Who is/was taking the medication
derivedFrom		0..*	Reference(Any)	Additional supporting information
taken	?! Σ	1..1	code	y | n | unk | na MedicationStatementTaken (Required)
reasonNotTaken	I	0..*	CodeableConcept	True if asserting medication was not given SNOMED CT Drugs not taken/completed Codes (Example)
reasonCode		0..*	CodeableConcept	Reason for why the medication is being/was taken Condition/Problem/Diagnosis Codes (Example)
reasonReference		0..*	Reference(Condition | Observation)	Condition or observation that supports why the medication is being/was taken
note		0..*	Annotation	Further information about the statement
dosage		0..*	Dosage	Details of how medication is/was taken or should be taken

Figure 23: Representation of the MedicationStatment resource [73]

In this concrete topic, the ”Encounter” is the resource of interest.

An ”Encounter” in FHIR can be used to represent a visit to the patient. A major issue here, however, is that it is currently hardly possible in FHIR to reference from a ”ResearchStudy” to ”Encounter” or vice versa. As study visits, however, are a fundamental concept, the common sense of needing this reference is obvious. The chain of resources, representing the clinical trials, have to be enlarged by a reference towards ”Encounters”. If this reference would be available, possible Chains would be:

1) *ResourceStudy* → *PlanDefinition* → *ActionDefinition* → *ActivityDefinition*

2) *ResourceStudy* → *Encounter* → *MedicationRequest*

3) *ResourceStudy → Encounter → MedicationStatement*

With these possible concatenations of resources, the study medication of patients, as well as the doses can be modeled. Also, the regular study visits can be represented in the different ”Encounter” resources, providing general information about the individual status of a patient during the study, as well concrete information about the specific medication for the patient through the ”MedicationRequest” and ”MedicationStatement” resources.

Focusing now on ”Encounter”, different elements such as the status, the type, a subject, and participants can be depicted. What is striking about this resource is, that is doesn't support a link towards any of the previously mentioned elements in the resource chain. However, as shown in the example chains before, ”Encounter” is not necessarily the last element inside the chain.

We now move on to the mentioned resources relevant for the clinical trial. Patients, Practitioner, and others can be linked out of ”Encounter” but are not taken into closer view at this point.

Name	Flags	Card.	Type	Description & Constraints
Encounter			DomainResource	An interaction during which services are provided to the patient Elements defined in Ancestors: id, meta, implicitRules, language, text, contained, extension, modifierExtension
identifier	Σ	0..*	Identifier	Identifier(s) by which this encounter is known
status	?! Σ	1..1	code	planned | arrived | triaged | in-progress | onleave | finished | cancelled + EncounterStatus (Required)
statusHistory		0..*	BackboneElement	List of past encounter statuses
status		1..1	code	planned | arrived | triaged | in-progress | onleave | finished | cancelled + EncounterStatus (Required)
period		1..1	Period	The time that the episode was in the specified status
class	Σ	0..1	Coding	inpatient | outpatient | ambulatory | emergency + ActEncounterCode (Extensible)
classHistory		0..*	BackboneElement	List of past encounter classes
class		1..1	Coding	inpatient | outpatient | ambulatory | emergency + ActEncounterCode (Extensible)
period		1..1	Period	The time that the episode was in the specified class
type	Σ	0..*	CodeableConcept	Specific type of encounter EncounterType (Example)
priority		0..1	CodeableConcept	Indicates the urgency of the encounter v3 Code System ActPriority (Example)
subject	Σ	0..1	Reference(Patient | Group)	The patient ro group present at the encounter
episodeOfCare	Σ	0..*	Reference(EpisodeOfCare)	Episode(s) of care that this encounter should be recorded against
incomingReferral		0..*	Reference(ReferralRequest)	The ReferralRequest that initiated this encounter
participant	Σ	0..*	BackboneElement	List of participants involved in the encounter
type	Σ	0..*	CodeableConcept	Role of participant in encounter ParticipantType (Extensible)
period		0..1	Period	Period of time during the encounter that the participant participated
individual	Σ	0..1	Reference(Practitioner | RelatedPerson)	Persons involved in the encounter other than the patient
appointment	Σ	0..1	Reference(Appointment)	The appointment that scheduled this encounter
period		0..1	Period	The start and end time of the encounter
length		0..1	Duration	Quantity of time the encounter lasted (less time absent)
reason	Σ	0..*	CodeableConcept	Reason the encounter takes place (code) Encounter Reason Codes (Preferred)
diagnosis	Σ	0..*	BackboneElement	The list of diagnosis relevant to this encounter

Figure 24: Representation of the Encounter resource [74]

Comparing all previously mentioned resources, especially the ”ResearchStudy” (figure 17) as well as the ”Encounter” resource (figure 24), no reference connecting ”Encounter” with the existing resource chain can be recognized.

To follow the goal of obtaining the possibility to represent study visits in the wanted form, creating this reference is taken into closer consideration in the following chapter.

5.1.3. Customization to achieve structured Study Representation

With the problem statement laid out in the previous section (chapter 5.1.2), we set out to define a solution approach. It seemingly will require the construction of a reference between "ResearchStudy" and "Encounter".

However, before we elaborate on this solution a certain aspect of FHIR has to be pointed out. Since FHIR is an international and relatively detailed standard, modeling extensions can't be done right away. It's essential to discuss proposed changes, for example in the form of extensions, with the FHIR community to provide a common knowledge and ensure not to make changes at unfavorable resources for the specific use case.

The best focal point for a useful discussion is the official FHIR chat[14]. All kind of developers, manager, and people working with FHIR are exchanging about different aspects and topics on this platform.

This concrete solution of planning an extension of FHIR by building a reference from "ResearchStudy" towards "Extension" was proposed in that forum and it turned out to be the wrong approach. This can be explained by having a look at the "ResearchStudy" and its purpose.

As mentioned previously, the current resource chain builds an abstract model of the study focusing on the study itself an not on the patient. Taking a closer look at the resources, none have any direct references towards a particular patient, keeping them on a highly abstract and theoretical level.

However, focusing on "Encounter", it refers towards a concrete patient and describing particular circumstances. By referencing from "ResearchStudy" towards "Encounter", the abstract level of the clinical trial would be violated.

Figure 25 is, therefore, to be taken as a wrong approach, since this representation of the "ResearchStudy" resource is doing precisely what was mentioned before; breaking through the abstract level by adding concrete, patient-related, information.

[14]The official FHIR chat in the form of a Zulip-platform is reachable on https://chat.fhir.org

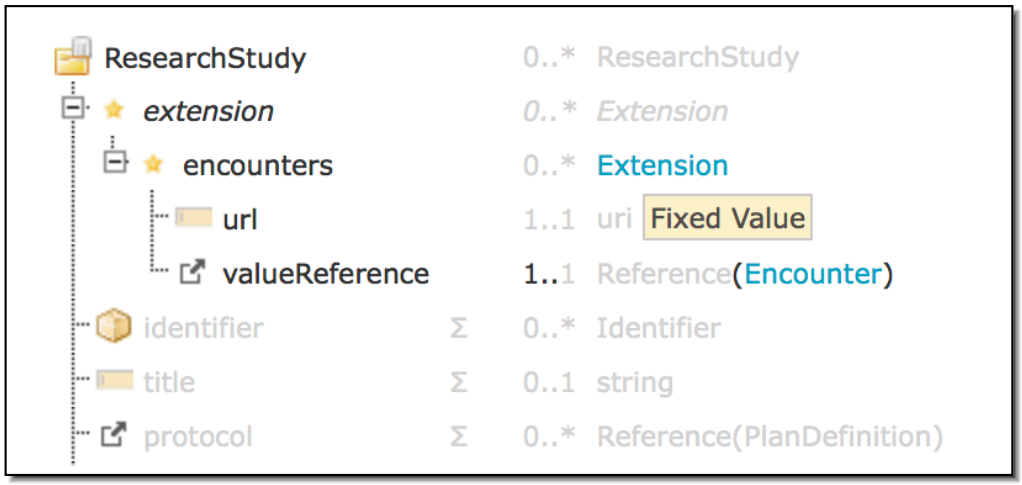


Figure 25: Semantical bad example of an extension

A semantically better way of creating an extension is, to create a link from the specification (in this case "Encounter") towards the abstract level of resources. This is a definite example of how quickly mistakes can be made if not all possible solutions are explored sufficiently.

Once a semantically correct solution approach has been found, we use the Forge tool to be sure to develop a syntactically correct external extension which is valid for integrating later on into resources.

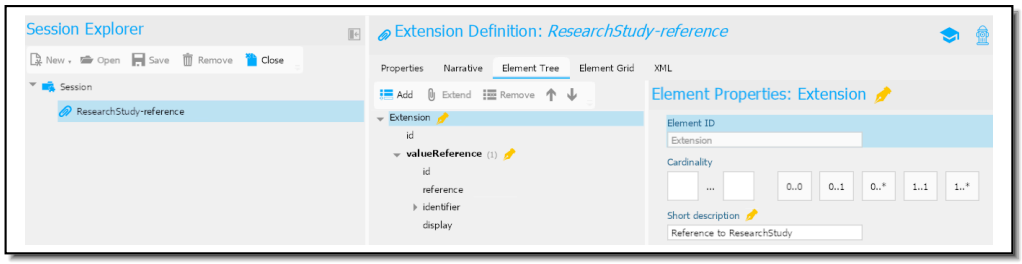


Figure 26: Creating an extension in Forge

The figure 26 shows the creation of an extension with the help of firely's tool Forge.

Even though the extension could also be created with plain JSON or XML, the graphical user interface supports the developer, for example with a syntax check while building the extension. The essential parts of the extension as an XML-File, as well as the extension-table, can be found in the appendix (appendix F).

The results of creating the extension with Forge are shown in figure 27. It is illustrating a reference to the "ResearchStudy" resource, just as planned.

The field "url" is a fixed value, pointing towards the online location of the extension. It is always necessary for an extension to have this field (therefore Forge is adding it automatically) to enable an application to download the extension to process it automatically.

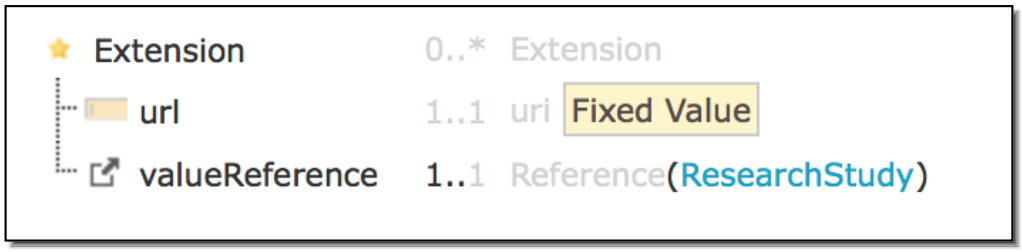


Figure 27: Extension representing a reference towards the ResearchStudy resource

Since having this extension alone doesn't enable the "Encounter" resource to refer to the clinical trial, a profile has to be created. Figure 28 shows the integration of the "Extension" into the "Encounter" resource.

Important to notice is that an open modeling approach has been selected to enable a natural use of "Encounter". Only when a particular reference is needed, it can be added towards the "Encounter.basedOn" attribute.

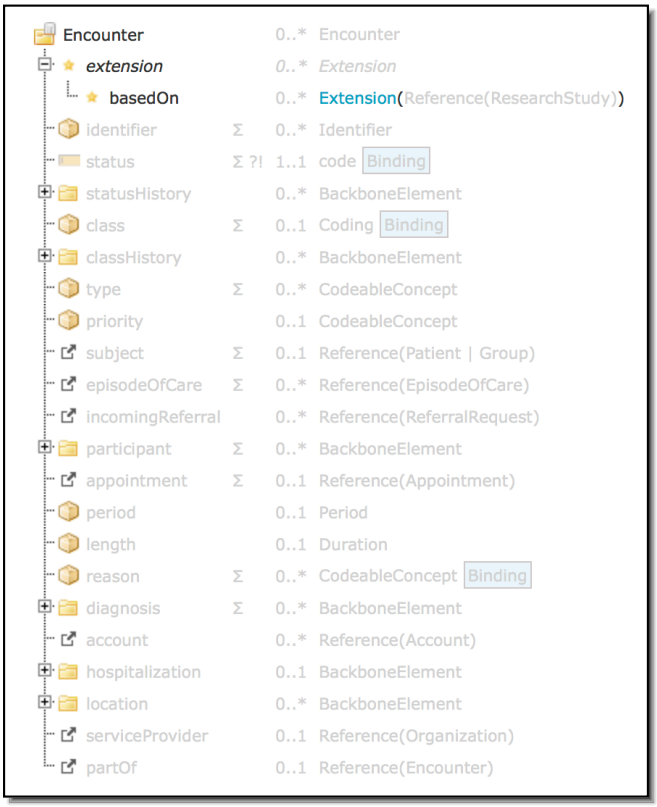


Figure 28: A profil of the Encounter resource, enhanced by an Extension

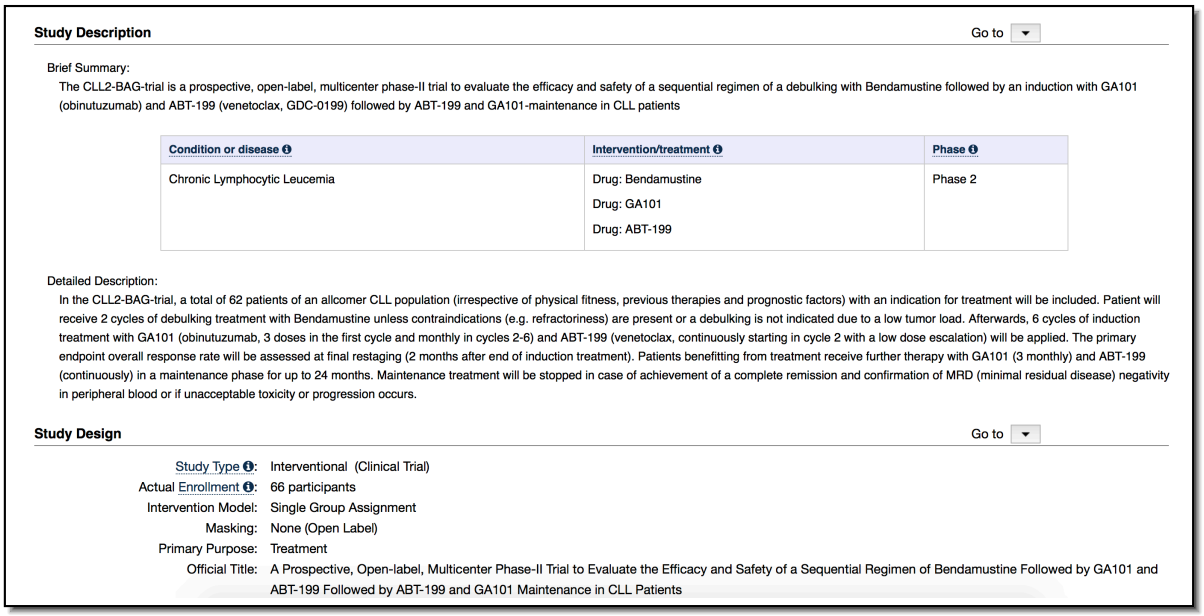
Concluding, using this profile, a reference from visits towards clinical trials is made possible. Furthermore, the resource can generally be used, no matter if a reference towards the "ResearchStudy" is provided or not.

Assumed the reference is made, it is possible to request all ”Encounters” of an active study, even though no reference from the trial towards the visits is given. This can be achieved via the FHIR search framework and the so-called, reverse chaining concept of FHIR. Since it’s no actual topic inside this thesis, the concept isn’t explained further[15].

5.1.4. Proof of Concept

After discussing the representation of clinical trials in FHIR and pointing out current problems, the following subchapter deals with the proof of concept of the reference chain, as well as the extension added to the ”Encounter” resource.

Establishing a situation to test the resources FHIR is providing, a real clinical study which Systems R&D are providing infrastructure for, is taken as a use case to build resources. We specifically take the CLL2-BAG study (part of it depicted in figure 29).



Study Description Go to

Brief Summary:
The CLL2-BAG-trial is a prospective, open-label, multicenter phase-II trial to evaluate the efficacy and safety of a sequential regimen of a debulking with Bendamustine followed by an induction with GA101 (obinutuzumab) and ABT-199 (venetoclax, GDC-0199) followed by ABT-199 and GA101-maintenance in CLL patients

Condition or disease	Intervention/treatment	Phase
Chronic Lymphocytic Leucemia	Drug: Bendamustine Drug: GA101 Drug: ABT-199	Phase 2

Detailed Description:
In the CLL2-BAG-trial, a total of 62 patients of an allcomer CLL population (irrespective of physical fitness, previous therapies and prognostic factors) with an indication for treatment will be included. Patient will receive 2 cycles of debulking treatment with Bendamustine unless contraindications (e.g. refractoriness) are present or a debulking is not indicated due to a low tumor load. Afterwards, 6 cycles of induction treatment with GA101 (obinutuzumab, 3 doses in the first cycle and monthly in cycles 2-6) and ABT-199 (venetoclax, continuously starting in cycle 2 with a low dose escalation) will be applied. The primary endpoint overall response rate will be assessed at final restaging (2 months after end of induction treatment). Patients benefitting from treatment receive further therapy with GA101 (3 monthly) and ABT-199 (continuously) in a maintenance phase for up to 24 months. Maintenance treatment will be stopped in case of achievement of a complete remission and confirmation of MRD (minimal residual disease) negativity in peripheral blood or if unacceptable toxicity or progression occurs.

Study Design Go to

Study Type: Interventional (Clinical Trial)
Actual Enrollment: 66 participants
Intervention Model: Single Group Assignment
Masking: None (Open Label)
Primary Purpose: Treatment
Official Title: A Prospective, Open-label, Multicenter Phase-II Trial to Evaluate the Efficacy and Safety of a Sequential Regimen of Bendamustine Followed by GA101 and ABT-199 Followed by ABT-199 and GA101 Maintenance in CLL Patients

Figure 29: Example extract of the CLL2-BAG study [64]

In order to keep the resources compact, not all possible data of the rather big complex study is shown. The focus is set on proving the possible references between the different focus points instead.

Clinical trials generally separate into different epochs - which are high-level time phases in a trial, and cycles which refer through the medication phases of the trial. Usually, visits are laid out along the individual phases. Figure 30 shows a different kind of data for each phase. Besides the medication, we have tests to confirm the effect and events which are

[15]Further Information about searching in FHIR and reverse chaining can be found here: https://www.hl7.org/fhir/http.html#search

observed in detail in order to detect any adverse effects. We also note that concomitant medication is also documented in order to infer any unreported side effects which are trying to be managed by the physician and could be caused by the investigational drug. Taking the investigational medication as an example, the ”GA101” antibody is given at day 1, day 2 and day 8 of the study, according to the doses displayed in the picture.

The second medication of interest in this scenario is the ”ABT-199” - also a monoclonal antibody.

Those two medications and the doses were taken as the example to include into different ”ActivityDefinitions” (appendix G.3).

Figure 30: Clinical Details for Cycle 1 of the CLL2-BAG

However, starting to create a study is typically done by building a ”ResearchStudy” resource (appendix G.1). In this case, the study was assigned the id ”researchstudy-soa-1”. Different fields of the resource are referencing onto the trial definition on the ”clinicalsite.org” trial management system.

The trial start date was set to the 6th May 2015, starting with the recruitment of participants. Sponsor and participalInvestigator are relating to the University Hospital of Cologne and Dr. med. Paula Cramer as principal investigator.

Moving down the chain, a reference towards the study protocol is made inside the ”ResearchStudy.protocol” field. This reference is set towards the ”PlanDefintion” with the id ”plandef-soa-1” (appendix G.2).

Starting by providing general information, such as the version of the protocol, the name, and the status; the study protocol resource has the flag ”experimental” set to true. This indicates that it is just for testing purposes and cannot be used for a real trial. Beside some other general information, the ”PlanDefinition.action” is mainly set into focus. For this proof of concept, two different actions have been defined, both referencing straight onto previously mentioned activities (appendix G.3).

Since the ”ActivityDefinition” resource can be used to create a generic concept of medications and doses during the study: ”GA101” and ”ABT-199” (shown in figure 30) are defined with some sample doses in these resources. The timing and the quantity, just as the repeating events for ”ABT-199”, are listed as examples and not in every detail.

Next up in the resource chain is the ”Medication” (appendix G.4). The essential data to mention here is the code and the form, both of which refer to the coding system SNOMEDCT. Otherwise, these resources have the required id and a status, setting them both to ”active”.

Working together closely with the medicine definition itself is the ”MedicationStatement” G.7) and the ”MedicationRequest” (appendix G.6). Starting with the statement, the ”MedicationStatementbasedOn”-attribute refers to a ”MedicationRequest”, and the context is defining the ”Encounter” in which the medication was asserted.

We should also mention the apparent reference towards the medication and the patient to receive their doses, as well as the reference to the treatment itself. Note that this resource always needs the ”taken”-attribute to show whether the patient has taken the investigational substance.

When talking about the ”MedicationRequest”, many things are similar to the ”MedicationStatement”. However, the request doesn’t contain a date where taking the substance was asserted but a period, visualizing the timestamp when the request for medication was authored. Other then the ’taken’ attribute, this resource is carrying an ’intent’ and can refer to a requester of the medication.

Last but not least, the customized resource ”Encounter” was filled with some sample data such as a status, a class, a subject, and a participant.

Most importantly, the ”extension” attribute has an ”url” pointing to the particular extension. In this specific case, it is the private simplifier project of the author and the creator of the extension. The ”reference value” is pointing towards the clinical study - ”researchstudy-soa-1” - also displaying the name.

5.2. Software Approaches and Improvements

Taking into consideration that machine-parsable data, in the form of FHIR resources, is raised during the study, it opens up way more possibilities for software-based assistance. FHIR applications are commonly evolving and given the fact that clinical trials at the Medical Systems R&D group are already using software solutions planning their studies, it should be possible to improve these systems by adding and adjusting functionality.

Developing a solution onto an FHIR backend can be the same as building upon a classical data warehouse structure for example. The process of development won't change very much. A positive feature, however, is that FHIR is also not going to exacerbate the process further. [75]

The significant changes in developing an application with an FHIR backend aren't coming from the choice of programming languages but when the application starts working with data. Since FHIR has a far and in-depth developed data model, no custom data structures have to be conceptualized and designed. If some of the data doesn't fit into the open data model, the answer in FHIR is to create profiles to alter the resources to accommodate with the data.

Talking about a concrete example, the idea of creating an automatic comparison between the medication planned for the study (defined in the "ActivityDefinition"), the medication for the particular patient (depicted in the "MedicationRequest") and the medication actually taken by the patient (logged through the usage of a "MedicationStatement" resource) is definitely a step into the right direction.

Such systems would not only be able to communicate and exchange data efficiently, thanks to the interoperability of FHIR resource, but also enrich the medical assistance of the patients because the data could be available for the responsible practitioners way faster.

6. Conclusion

The project of mapping clinical trials and protocols to FHIR resources is still in progress and will go on after the work on this thesis is finished.

So far, the concept of profiling in FHIR is a well-defined process. Concepts of clinical studies in FHIR, however, are quite new and for such a complex topic the amount of information that needs to be modeled and mapped isn't trivial.

Though FHIR is continually improving concepts in respect of clinical trials, at closer look at the maturity levels of the resources used, it's evident that the resources are still improving. The HL7 organization has stated that the standard is going to expand further for trials and their documentation on the next release of FHIR. Since the 2015 publication, a lot has changed and one of the achievements of the project was to gain an overview of FHIR's resources for a mapping proposal. My personal understanding of FHIR itself and clinical trials is one of the most significant achievements. A first approach of profiling the resources to the needs of Clinical Trials has been achieved.

What follows is a personal conclusion derived in the form of a lessons learned during the project. This opinion does not claim to be impartial.

It also seems fitting to give a future outlook of where to move on beyond the project in order to achieve a full representation of clinical trials in the form of FHIR resources.

Also, new developments in FHIR offer exciting new possibilities in the way clinical trials could be conducted in the future - specifically with regards to extracting source data relevant for research from primary systems (e.g., EMR).

6.1. Lessons learned and Results

At the end of this thesis one should sum up the main issues encountered and solution approaches which were developed. In general, I would note that the conceptual model of clinical trials has not yet matured sufficiently in FHIR but that given the right approaches, these can be discussed and reviewed at a surprising pace so as to make their way into the standard relatively quickly.

Regarding the maturity of the present model, for instance, modifying planned medication schedules for trials subjects is still very cumbersome to model. In this concrete case, the "CarePlan" resource can be considered as a representation of the abstract plan or schedule.

However, presently – even following a long discussion on chat.fhir.org – it is not possible to assign that schedule to a concrete study subject with the existing resources. Even for such a basic concept, one has to write a custom extension.

In this case, you could potentially establish a relationship between schedule and subject via reverse chaining. However, the approach would not be feasible in practice since with several existing CarePlans there is no means of defining ‚the authoritive' plan for the study subject.

The specific issue of referencing from visits in a trial, in the form of the „encounter" resource is an excellent example of how the standard can evolve given the right approach suggestions: The extension developed for this project was seen as a clear necessity and was quickly proposed to be adopted in coming releases.

6.2. Future Outlook

So far, only a very narrow domain in search of a solution approach of mapping the clinical trial to resources could be covered. However, the "visit" and "schedule" concepts are fundamental for clinical trials and a machine-readable format for these concepts is of great value.

The research on the current representation of clinical trials in FHIR resources has shown, that HL7 and FHIR are still continually evolving their resources, pushing them to higher maturity levels and react to the needs of the clinical institutions. One has to state that the speed at which this work is evolving is very promising compared to previous standards - such as CDISC PRM, supposedly dedicated to clinical trials, which in 10 years did not deliver any significant value towards a machine-readable clinical trial protocol.

The general framework of FHIR itself is evolving and making itself extremely valuable for clinical research. A recent article by Grahame Grieve suggests using Questionnaires in FHIR not only as a form template but as a query template which can search the appropriate FHIR resources and pass on the values back and populate any identified values automatically from source systems (appendix H). This sounds like science fiction, but in fact, the concept and experimental tooling building on top of FHIR path will be balloted during this years' Hl7 meeting in Baltimore in November.

The value of this framework for - say identifying participants for a clinical trial or retrieving source data to the research database is a quantum leap in converging health care and clinical research. [76]

A. Appendix: RESTful API

A.1. Create a Resource

Starting with creating an example resource of a Patient by sending a POST request to the FHIR-Server.

Listing 1: Create a resource

```
POST [base]/Patient

{
  "resourceType": "Patient",
  "text": {
    "status": "testing patient",
    "div": "<div>...</div>"
  },
  "active": true,
  "name": [
    {
      "use": "official",
      "family": "Doe",
      "given": [
        "John",
        "Sam"
      ]
    }
  ],
  "managingOrganization": {
    "reference": "Organization/1"
  }
}
```

A.2. Read a Resource

Reading the Patient with the id 1, using the HTTP-GET request to the FHIR-Server. The second call is also reading the patient, but with requesting JSON as the particular format of the data.

Listing 2: Read a Resource

```
GET [base]/Patient/1

GET [base]/Patient/1?_format=json
```

A.3. Delete a Resource

Deleting the Patient resource with the logical_id ”1”.

Listing 3: Delete a resource

```
DELETE [base]/Patient/1
```

A.4. Update a Resource

Updating an existing Patient resource by sending a HTTP-PUT request to the FHIR Server. The Patient is sent fully and with some exchanged data.

Listing 4: Update a resource

```
PUT [base]/Patient/1

{
  "resourceType": "Patient",
  "id":"example",
  "text": {
    "status": "changed testing patient",
    "div": "..."
  },
  "active": false,
  "name": [{
      "use": "official",
      "family": "Doe",
      "given": [
        "John",
        "Sam"
    ]}
  ],
  "birthDate": "1991-01-27",
  "managingOrganization": {
    "reference": "Organization/1"
  }
}
```

B. Appendix: Conformance Statement

The beginning of the Conformance Statement contains information about the publisher and metadata about the server. The Conformance Statement is taken from firely, by requesting it using http://vonk.fire.ly/metadata.

Listing 5: Conformance Statement

```
<CapabilityStatement xmlns="http://hl7.org/fhir">
<id value="a4155e86-dfb8-42b4-b5dd-d37c771667d6" />
<meta>
    <versionId value="3e62ad30-84c9-4e8a-afea
       -167694875901" />
    <lastUpdated value="2018-07-21T21:29:01.507+00:00" />
</meta>
<language value="en-US" />
<url value="metadata" />
<version value="0.1" />
<name value="Vonk beta conformance" />
<status value="active" />
<experimental value="true" />
<date value="2018-07-21T21:29:01.507+00:00" />
<publisher value="Firely" />
<contact>
    <name value="Licensed to" />
    <telecom>
        <system value="email" />
        <value value="vonk@fire.ly" />
        <use value="work" />
    </telecom>
</contact>
[...]
```

C. Appendix: Approval of Clinical Trials

C.1. Approval Process for Drugs and Biologics

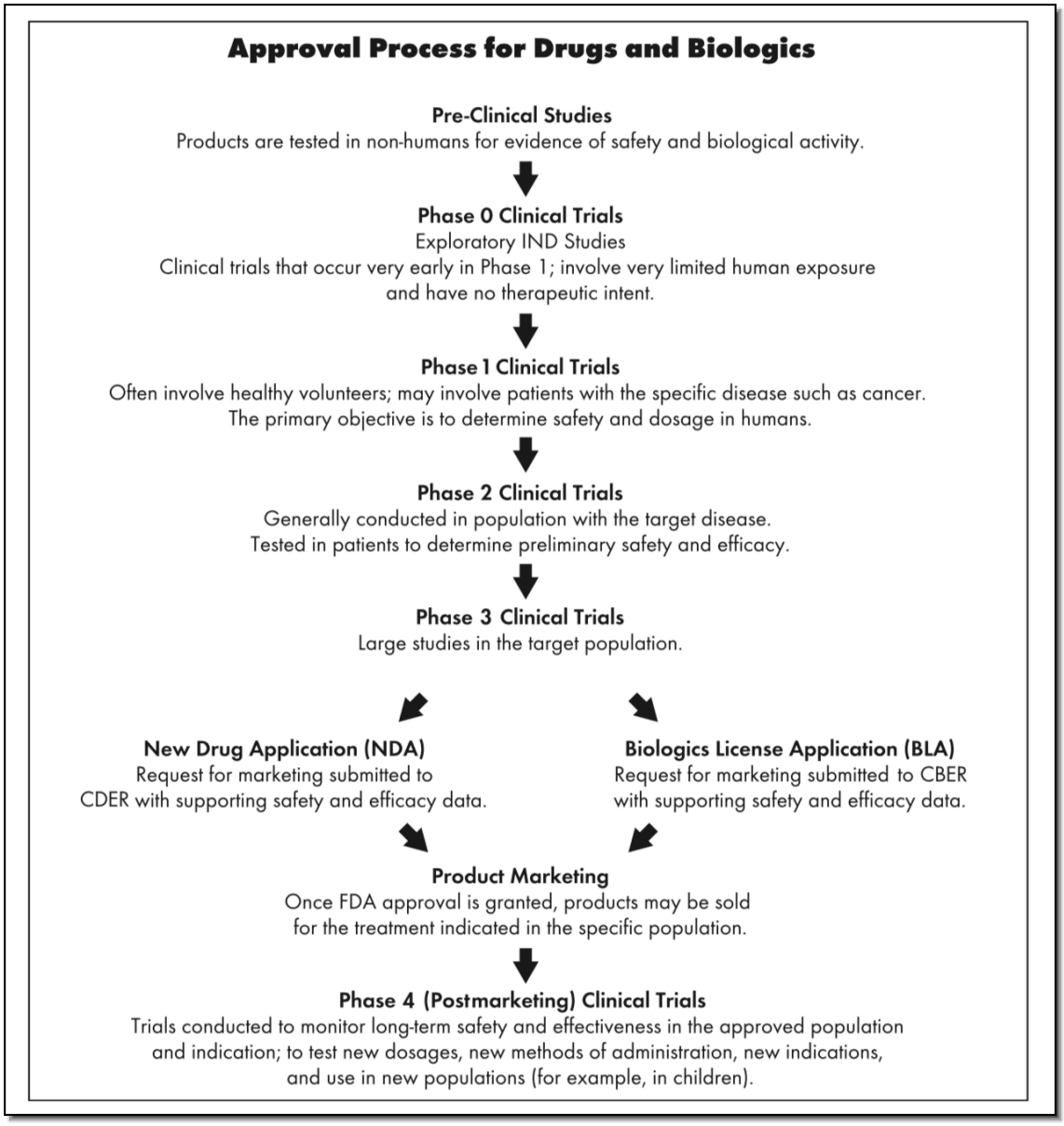


Figure 31: Approval process for drugs and biologics [47]

C.2. Approval Process for Devices

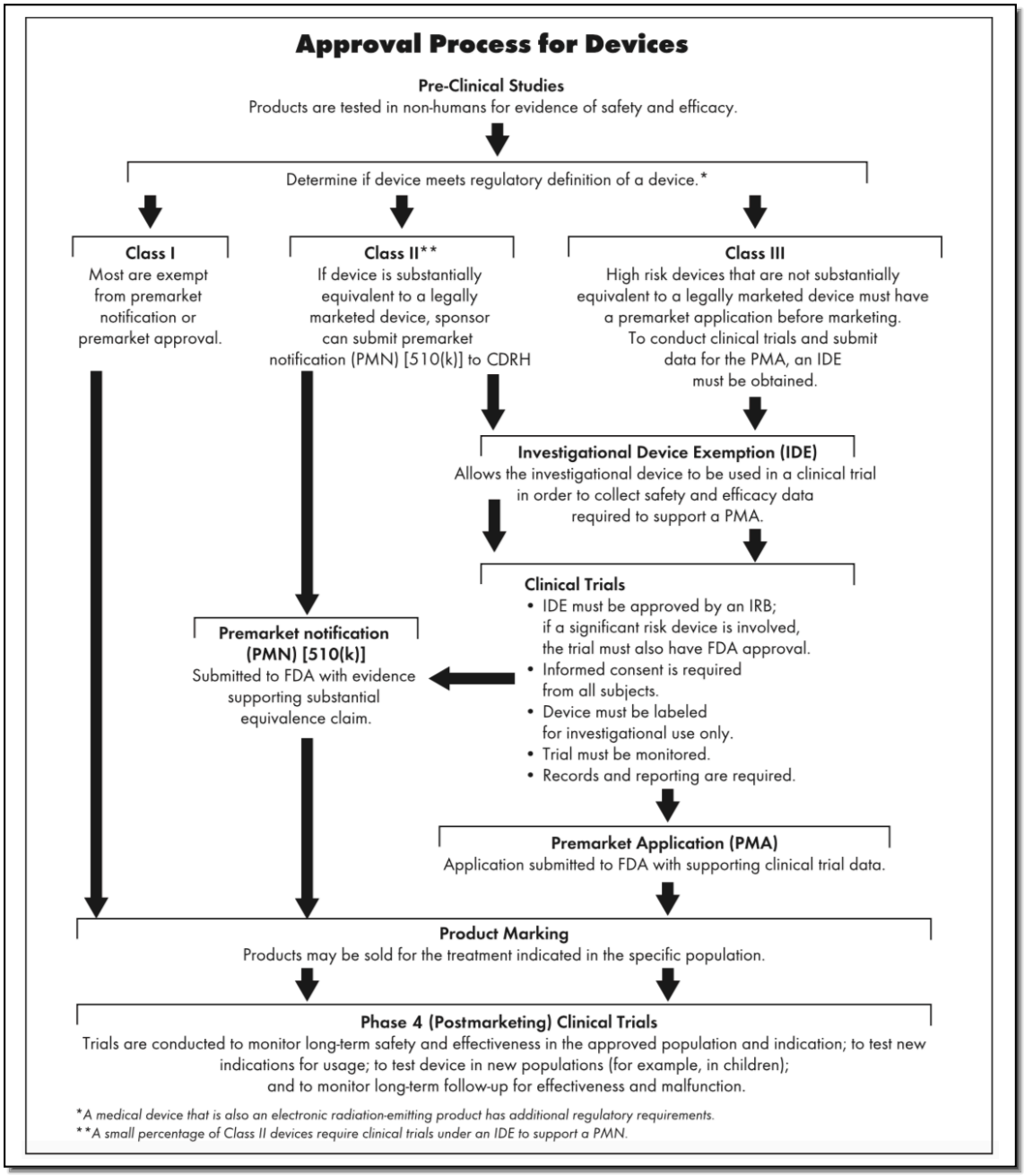


Figure 32: Approval process for devices [47]

D. Appendix: Example Profiles

D.1. DE-Baseprofile Patient

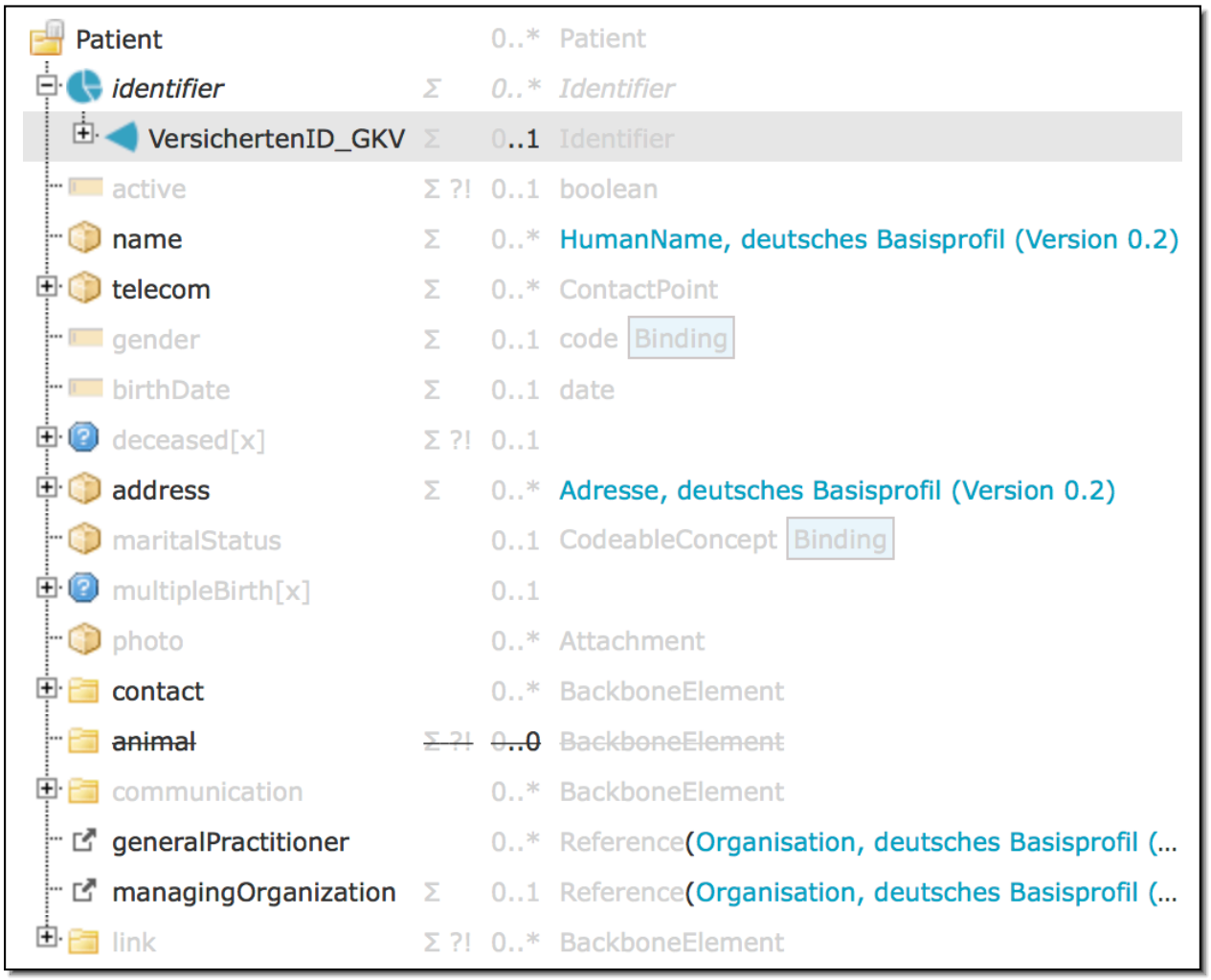


Figure 33: DE-Baseprofile Patient [77]

D.2. DE-Baseprofile Patient - JSON

The profile was cut, due to the amount of information and the length of the data[16].

Listing 6: DE-Baseprofile Patient

```
{
    "resourceType":"StructureDefinition",
    "meta":{
        "lastUpdated":"2017-12-05T18:56:51.686+01:00"
    },
    "url":"http://fhir.de/StructureDefinition/patient-de-
       basis/0.2",
    "version":"0.2-WORK",
    "name":"patient-de-basis-0.2",
    "title":"Patient, deutsches Basisprofil (Version 0.2)
       ",
    "status":"draft",
    "date":"2018-06-18",
    "publisher":"HL7 Deutschland e.V. (Technisches Komitee
       FHIR)",
    "contact": [
        [...]
    ],
    "description":"Basisprofil für die Verwendung der
       Patient Ressource in Deutschland ",
    "copyright":"HL7 Deutschland e.V.",
    "fhirVersion":"3.0.1",
    "mapping": [
        {
            "identity":"KVDT",
            "name":"KVDT Mapping"
        },
    [...]
```

[16]The full profile can be viewed at https://simplifier.net/BasisprofilDE/patient-de-basis-0.2/~json

D.3. NL-Baseprofile Patient

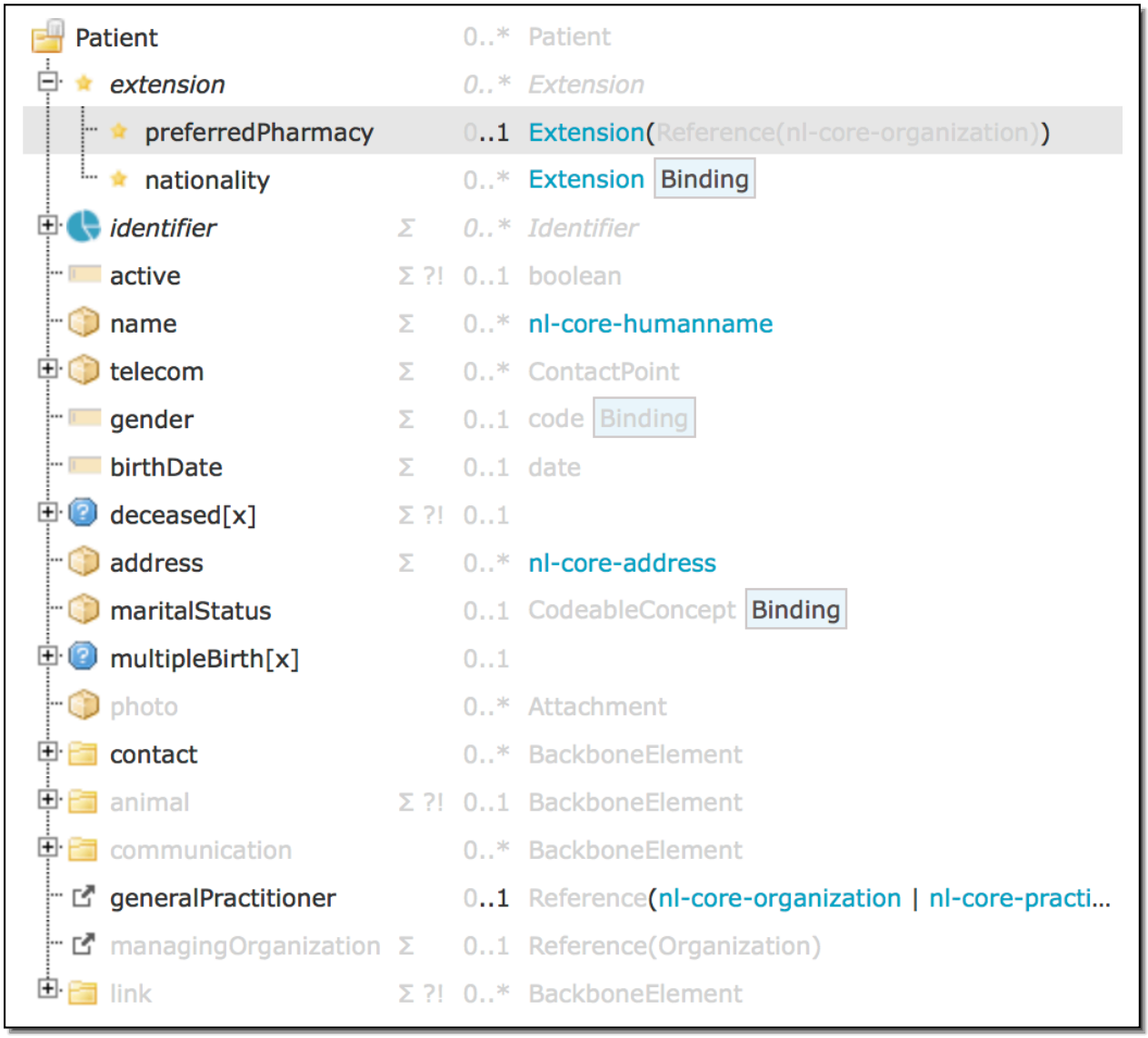


Figure 34: NL-Baseprofile Patient [78]

D.4. NL-Baseprofile Patient - JSON

The profile was cut, due to the amount of information and the length of the data[17].

Listing 7: NL-Baseprofile Patient

```
{
    "resourceType":"StructureDefinition",
    "id":"nl-core-patient",
    "meta":{
        "versionId":"15",
        "lastUpdated":"2017-01-23T13:46:49.591+00:00"
    },
    "url":"http://fhir.nl/fhir/StructureDefinition/nl-core
      -patient",
    "version":"1.0",
    "name":"nl-core-patient",
    "title":"nl-core-patient",
    "status":"retired",
    "publisher":"HL7 Netherlands",
    "contact": [...],
    "description":"A Patient resource as defined by the
      Dutch Health and Care Information models or HCIM (
      Dutch: Zorginformatiebouwsteen or ZIB) Patient, with
       additions from the HCIMs Nationality, MaritalStatus
      , ContactPerson, HealthProfessional and
      HealthcareProvider (HCIM releases 2015, 2016 and
      2017)",
    "purpose":"Patient. Tracking a patient is the center
      of the healthcare process. Names and addresses are
      also in compliance with HL7 V3 Basic Components.",
    "copyright":"CC0",
    "fhirVersion":"3.0.1",
    [...]
```

[17]The full profile can be viewed at https://simplifier.net/NictizSTU3/nl-core-patient/~json

D.5. DE-Baseprofile Organisation

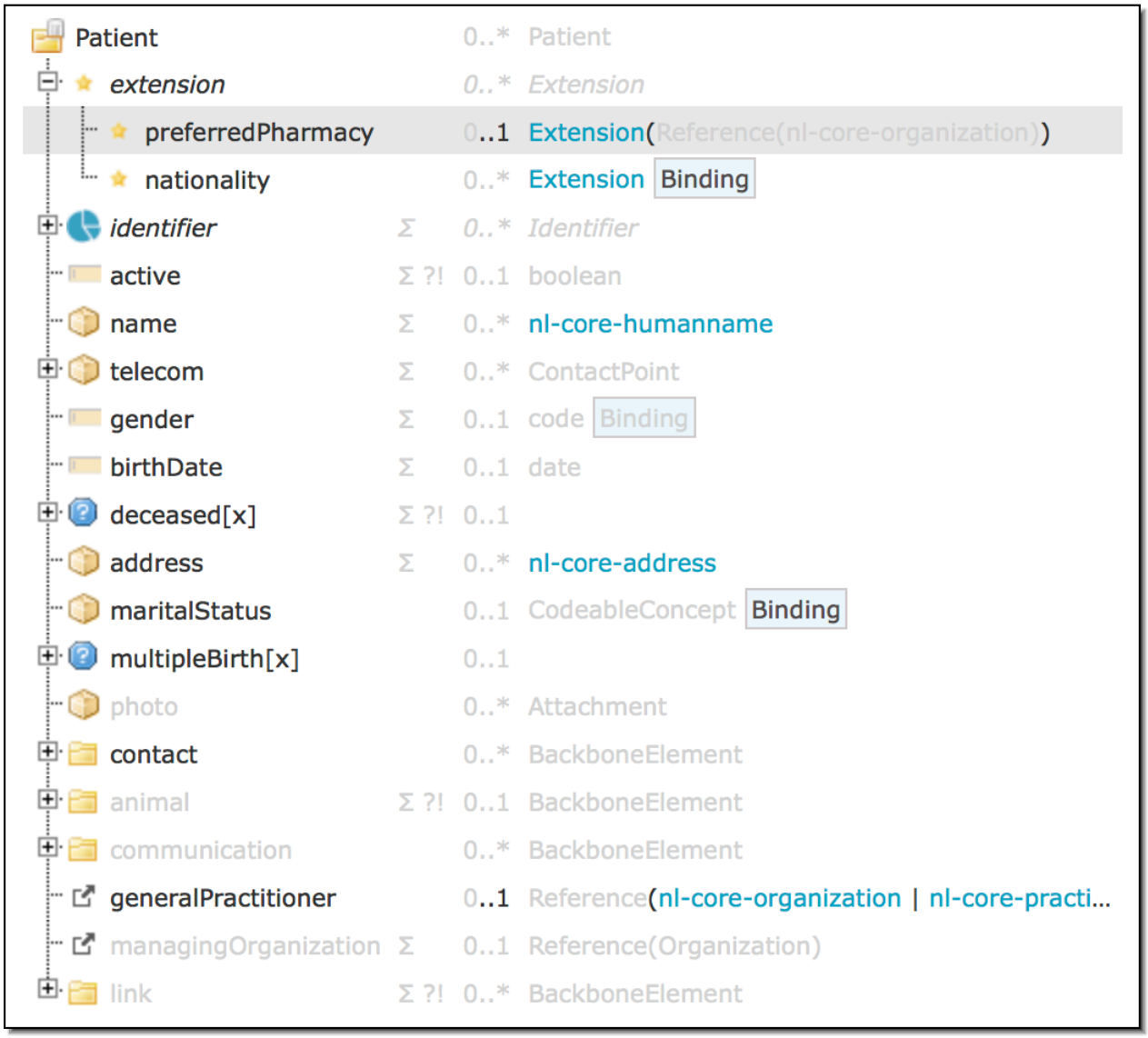


Figure 35: NL-Baseprofile Patient [78]

D.6. DE-Baseprofile Organisation - JSON

The profile was cut, due to the amount of information and the length of the data[18].

Listing 8: DE-Baseprofile Organisation

```
{
    "resourceType":"StructureDefinition",
    "meta":{
        "lastUpdated":"2017-10-20T11:01:15.167+02:00"
    },
    "url":"http://fhir.de/StructureDefinition/organization
       -de-basis/0.2",
    "version":"0.2-WORK",
    "name":"organization-de-basis-0.2",
    "title":"Organisation, deutsches Basisprofil (Version
       0.2)",
    "status":"draft",
    "date":"2018-06-28",
    "publisher":"HL7 Deutschland e.V. (Technisches Komitee
       FHIR)",
    "contact": [
        {
            "telecom": [
                {
                    "system":"other",
                    "value":"http://hl7.de/technische-
                       komitees/fhir/"
                }
            ]
        }
    ],
    "description":"Basisprofil für die Verwendung der
       Organization Ressource in Deutschland.",
    [...]
    }
}
```

[18]The full profile can be viewed at https://simplifier.net/BasisprofilDE/organization-de-basis-0.2/~json

E. Appendix: Slicing Example

The following example was taken out of the Simplifier Profiling Academy [46].

Listing 9: Slicing Example

```
<element id="MedicationStatement.subject">
    <path value="MedicationStatement.subject"/>
    <slicing>
        <discriminator>
            <type value="type"/>
            <path value="$this"/>
        </discriminator>
        <rules value="open"/>
    </slicing>
    <min value="1"/> <max value="1"/>
</element>
<element id="MedicationStatement.subject:SubjectPatient">
    <path value="MedicationStatement.subject"/>
    <sliceName value="SubjectPatient"/>
    <min value="0"/> <max value="1"/>
    <type>
        <code value="Reference"/>
        <targetProfile value="http://hl7.org/fhir/
            StructureDefinition/Patient"/>
    </type>
</element>
<element id="MedicationStatement.subject:SubjectGroup">
    <path value="MedicationStatement.subject"/>
    <sliceName value="SubjectGroup"/>
    <min value="0"/> <max value="1"/>
    <type>
        <code value="Reference"/>
        <targetProfile value="http://hl7.org/fhir/
            StructureDefinition/Group"/>
    </type>
</element>
```

F. Appendix: Customized Resource and Extension

Encounter		..
.extension		..
.extension.basedOn	Extension	..1

Table 7: Profiling table of the ”Encounter” profile

Listing 10: Differential of "Encounter" resource

```
<differential>
        <element id="Encounter.extension">
            <path value="Encounter.extension" />
            <slicing>
                <discriminator>
                    <type value="value" />
                    <path value="url" />
                </discriminator>
                <rules value="open" />
            </slicing>
        </element>
        <element id="Encounter.extension:MyExtension">
            <path value="Encounter.extension" />
            <sliceName value="basedOn" />
            <short value="Optional Extensions Element" />
            <definition value="Optional Extension Element
               - found in all resources." />
            <min value="0" />
            <max value="*" />
            <type>
                <code value="Extension" />
                <profile value="http://example.org/fhir/
                   StructureDefinition/MyExtension" />
            </type>
        </element>
    </differential>
```

G. Appendix: Proof of Concept

G.1. Appendix: Proof of Concept - ResearchStudy

Listing 11: Proof of Concept - ResearchStudy

```
<ResearchStudy>
    <id value="researchstudy-soa-1" />
    <meta>
        <profile value="http://clinicalsite.org/..." />
    </meta>
    <identifier>
        <system value="http://clinicalsite.org/..." />
        <value value="2157" />
    </identifier>
    <title value="CLL2-BAG" />
    <protocol>
      <reference value="PlanDefinition/plandef-soa-1" />
    </protocol>
    <status value="in-progress">
        <extension url="http://clinicalsite.org/...">
            <valueCode value="2" />
        </extension>
    </status>
    <period><start value="2015-05-06" /></period>
    <sponsor>
        <display value="Universität zu Köln" />
    </sponsor>
    <principalInvestigator>
        <display value="Dr. med. Paula Cramer" />
    </principalInvestigator>
    <site>
        <identifier>
            <system value="http://clinicalsite.org/..." />
            <value value="53" />
        </identifier>
    </site>
</ResearchStudy>
```

G.2. Appendix: Proof of Concept - PlanDefinition

Listing 12: Proof of Concept - PlanDefinition

```
<PlanDefinition>
    <id value="plandef-soa-1" />
    <version value="1.00" />
    <name value="Study protocol for CLL2-BAG" />
    <status value="draft" />
    <experimental value="true" />
    <date value="2018-08-07" />
    <publisher value="Markus Döring" />
    <copyright value="Medical Systems R&D group" />
    <action>
        <title value="GA101" />
        <definition>
            <reference value="ActivityDefinition/
               plannedInvestigationalDrug1" />
            <display value="GA101" />
        </definition>
    </action>
    <action>
        <title value="ABT-199" />
        <definition>
            <reference value="ActivityDefinition/
               plannedInvestigationalDrug2" />
            <display value="ABT-199" />
        </definition>
    </action>
</PlanDefinition>
```

G.3. Appendix: Proof of Concept - ActivityDefinition

Listing 13: Proof of Concept - ActivityDefinition 1

```
<ActivityDefinition>
    <id value="plannedInvestigationalDrug1" />
    <name value="planned Investigational Drug GA101" />
    <status value="draft" />
    <experimental value="true" />
    <date value="2018-08-07" />
    <copyright value="Medical Systems R&D group" />
    <productReference>
        <reference value="Medication/investigationalDrug1"
            />
        <display value="GA101" />
    </productReference>
    <dosage>
        <text value="D1 mit 100mg" />
        <timing>
            <event value="2015-12-04" />
        </timing>
        <doseQuantity>
            <value value="100" />
        </doseQuantity>
    </dosage>
    <dosage>
        <text value="D2 mit 900mg" />
        <timing>
            <event value="2015-12-05" />
        </timing>
        <doseQuantity>
            <value value="900" />
        </doseQuantity>
    </dosage>
    ...
</ActivityDefinition>
```

Listing 14: Proof of Concept - ActivityDefinition 2

```
<ActivityDefinition>
    <id value="plannedInvestigationalDrug2" />
    <name value="planned Investigational Drug ABT-199" />
    <status value="draft" />
    <experimental value="true" />
    <date value="2018-08-07" />
    <copyright value="Medical Systems R&D group" />
    <productReference>
        <reference value="Medication/investigationalDrug2"
            />
        <display value="ABT-199" />
    </productReference>
    <dosage>
        <text value="D1-7 mit 20mg" />
        <timing>
            <event value="2016-01-07" />
            <repeat>
                <count value="7" />
                <frequency value="1" />
                <period value="1" />
                <periodUnit value="d" />
            </repeat>
        </timing>
        <doseQuantity>
            <value value="20" />
        </doseQuantity>
    </dosage>
    ...
</ActivityDefinition>
```

G.4. Appendix: Proof of Concept - Medication

Listing 15: Proof of Concept - Medication 1

```
<Medication>
    <id value="investigationalDrug1" />
    <code>
        <coding>
            <system value="http://snomed.info/sct" />
            <code value="710287009" />
            <display value="GA101" />
        </coding>
    </code>
    <status value="active" />
    <form>
        <coding>
            <system value="http://snomed.info/sct" />
            <code value="385229008" />
            <display value="IV-Infusion" />
        </coding>
    </form>
</Medication>
```

Listing 16: Proof of Concept - Medication 2

```
<Medication>
    <id value="investigationalDrug2" />
    <code>
        <coding>
            <system value="http://snomed.info/sct" />
            <code value="763511000" />
            <display value="ABT-199" />
        </coding>
    </code>
    <status value="active" />
    <form>
        <coding>
            <system value="http://snomed.info/sct" />
            <code value="385022006" />
            <display value="Oral liquid" />
        </coding>
    </form>
</Medication>
```

G.5. Appendix: Proof of Concept - Encounter

Listing 17: Proof of Concept - Encounter

```
<Encounter>
    <id value="studyvisit1" />
    <extension url="https://simplifier.net/test20171092/
       researchstudy-reference">
        <valueReference>
            <reference value="ResearchStudy/researchstudy-
               soa-1" />
            <display value="CLL2-BAG" />
        </valueReference>
    </extension>
    <status value="planned" />
    <class>
        <system value="http://hl7.org/fhir/v3/ActCode" />
        <code value="AMB" />
        <display value="ambulatory" />
    </class>
    <subject>
        <reference value="Patient/1" />
    </subject>
    <participant>
        <individual>
            <reference value="Practitioner/150" />
        </individual>
    </participant>
    <length>
        <value value="30" />
        <unit value="min" />
        <system value="http://unitsofmeasure.org" />
        <code value="min" />
    </length>
</Encounter>
```

G.6. Appendix: Proof of Concept - MedicationStatement

Listing 18: Proof of Concept - MedicationStatement

```
<MedicationStatement>
    <id value="medicationstatement1" />
    <basedOn>
        <reference value="MedicationRequest/
            medicationrequest1" />
    </basedOn>
    <context>
        <reference value="Encounter/studyvisit1" />
    </context>
    <status value="intended" />
    <medicationReference>
        <reference value="Medication/investigationalDrug1"
            />
    </medicationReference>
    <dateAsserted value="2018-08-09" />
    <subject>
        <reference value="Patient/1" />
    </subject>
    <taken value="y" />
</MedicationStatement>
```

G.7. Appendix: Proof of Concept - MedicationRequest

Listing 19: Proof of Concept - MedicationRequest

```
<MedicationRequest>
    <id value="medicationrequest1" />
    <definition>
        <reference value="ActivityDefinition/
            plannedInvestigationalDrug1" />
    </definition>
    <intent value="proposal" />
    <medicationReference>
        <reference value="Medication/investigationalDrug1"
            />
    </medicationReference>
    <subject>
        <reference value="Patient/1" />
    </subject>
    <authoredOn value="2018-08-09" />
    <requester>
        <agent>
            <reference value="Practitioner/150" />
        </agent>
    </requester>
</MedicationRequest>
```

H. Appendix: Active Questionnaire Example

An example Questionnaire, create by Simone Heckmann, for the University Hospital Cologne, based on the work of Grahame Grieve about active Questionnaires. [76]

Listing 20: Active Questionnaire Example

```
<Questionnaire xmlns="http://hl7.org/fhir">
  <url value="http://uni-koeln.de/fhir/Questionnaire/nNGM-
     active" />
  <title value="nNGM (active)" />
  <status value="draft" />
  <date value="2018-08-10" />
  <subjectType value="Patient" />
  <item>
  <extension url="http://hl7.org/fhir/StructureDefinition/
     variable">
      <valueExpression>
        <name value="smokeObs" />
        <language value="application/x-fhir-query" />
        <expression value="Observation?code=http://loinc.
           org|72166-2" />
      </valueExpression>
    </extension>
    <extension url="http://hl7.org/fhir/
       StructureDefinition/populate-value">
      <valueExpression>
        <language value="text/fhirPath" />
        <expression value="smokeObs.value" />
      </valueExpression>
    </extension>
    ...
  </item>
</Questionnaire>
```

List of Figures

List of Tables

References

[1] Systems R&D, *Strategische Investition zu einer effizienteren Informationsverarbeitung*, confidential, 2018.

[2] Ralph Kimball, *An Architecture for Data Quality*, 2007. [Online]. Available: http://www.kimballgroup.com/wp-content/uploads/2007/10/An-Architecture-for-Data-Quality1.pdf.

[3] HL7.org. (2017). Overview - FHIR v3.0.1, [Online]. Available: https://hl7.org/fhir/STU3/index.html (visited on 2018-03-09).

[4] J. C. Mandel, D. A. Kreda, K. D. Mandl, I. S. Kohane, and R. B. Ramoni, "Smart on fhir: A standards-based, interoperable apps platform for electronic health records.", *Journal of the American Medical Informatics Association*, 2016-02, ISSN: 1527-974X. DOI: 10.1093/jamia/ocv189.

[5] Gustav Vella, personal communication, 2018.

[6] Healthcare Language Blog. (2014). Understanding the Three Levels of Interoperability, [Online]. Available: http://blog.healthlanguage.com/understand-the-three-levels-of-interoperability (visited on 2018-04-23).

[7] Alliance for Health Reform, *High and rising costs of health care in the u.s. - the challenge: Changing the trajectory*, 2012. [Online]. Available: http://www.allhealthpolicy.org/wp-content/uploads/2017/03/Alliance_for_Health_Reform_121.pdf (visited on 2018-03-07).

[8] D. A. Conrad, "The theory of value-based payment incentives and their application to health care", *Health Services Research*, vol. 50, pp. 2057–2089, 2015. DOI: 10.1111/1475-6773.12408.

[9] H. Kubicek, R. Cimander, and H. Scholl, *Organizational Interoperability in E-Government*, 1st. Springer, 2011, pp. 185ff. ISBN: 9783642225017.

[10] GHSG. (2018). German hodgkin study group, [Online]. Available: https://en.ghsg.org (visited on 2018-08-08).

[11] Universität zu Köln. (2018). Forschung an der Fakultät, [Online]. Available: http://medfak.uni-koeln.de/forschung.html (visited on 2018-05-12).

[12] Maria Klein-Schmeink and Dr. Kirsten Kappert-Gonther and Kordula Schulz-Asche and Dr. Bettina Hoffmann and Katja Dörner and Dr. Anna Christmann and Kai Gehring and Erhard Grundl and Ulle Schauws and Kordula Schulz-Asche and Margit Stumpp and Beate Walter-Rosenheimer. (2018). Mangelnde Umsetzung von offenen internationalen Standards für den digitalen Informationsaustausch im deutschen

Gesundheitswesen (Interoperabilität), [Online]. Available: https://dipbt.bundestag.de/doc/btd/19/019/1901965.pdf (visited on 2018-05-28).

[13] F. Adebesin, R. Foster, P. Kotzé, and D. van Greunen, "A review of interoperability standards in e-health and imperatives for their adoption in africa", *South African Computer Journal No. 50*, 2013-07.

[14] Himss transforming health through information and technology, *Definition of interoperability*, 2013.

[15] IEEE, *Ieee standard computer dictionary a compilation of ieee standard computer glossaries*, 1990.

[16] D. Health, "Semantic interoperability unlocking the potential of digital health information", *360 Clinical Intelligence*,

[17] Patricia Gibbons, Noam Arzt, Susie Burke-Beebe, Chris Chute, , Gary Dickinson, Tim Flewelling, Thomas Jepsen, Don Kamens, Joanne Larson, John Ritter, Michael Rozen, Sherry Selover, Jean Stanford. (2007). Coming to Terms: Scoping Interoperability for Health Care, [Online]. Available: https://www.hln.com/assets/pdf/Coming-to-Terms-February-2007.pdf (visited on 2018-05-15).

[18] T. Benson and G. Grieve, *Principles of Health Interoperability*. Springer International Publishing, 2016. DOI: 10.1007/978-3-319-30370-3.

[19] H. van der Veer and A. Wiles, "Achieving technical interoperability - the etsi approach", *ETSI White Paper No. 3*, 2008-04.

[20] D. Broyles, B. E. Dixon, R. Crichton, P. Biondich, and S. J. Grannis, "The evolving health information infrastructure", in *Health Information Exchange*, Elsevier, 2016, pp. 107–122. DOI: 10.1016/b978-0-12-803135-3.00007-4.

[21] M. Hosseini and B. E. Dixon, "Syntactic interoperability and the role of standards", in *Health Information Exchange*, Elsevier, 2016, pp. 123–136. DOI: 10.1016/b978-0-12-803135-3.00008-6.

[22] EuropeanCommission. (2012). Discussion Paper on Semantic and Technical Interoperability, [Online]. Available: https://ec.europa.eu/health//sites/health/files/ehealth/docs/ev_20121107_wd02_en.pdf (visited on 2018-05-25).

[23] Patrik Sundberg and Eyal Oren. (2018). Making Healthcare Data Work Better with Machine Learning, [Online]. Available: https://ai.googleblog.com/2018/03/making-healthcare-data-work-better-with.html (visited on 2018-05-30).

[24] Apple. (2018). Apple announces effortless solution bringing health records to iPhone, [Online]. Available: https://www.apple.com/newsroom/2018/01/apple-announces-effortless-solution-bringing-health-records-to-iPhone/ (visited on 2018-05-30).

[25] Microsoft. (2018). HL7 FHIR on Azure: A Global Approach to Healthcare Interoperability, [Online]. Available: https://info.microsoft.com/HL7FHIROnAzure-Registration.html (visited on 2018-06-30).

[26] Ringholm. (2014). The early history of health Level 7, [Online]. Available: http://www.ringholm.de/docs/the_early_history_of_health_level_7_HL7.htm (visited on 2018-05-23).

[27] Corepoint Health. (2009). The HL7 Evolution. Comparing HL7 Version 2 to Version 3, Including a History of Version 2, [Online]. Available: https://corepointhealth.com/wp-content/uploads/hl7-history-v2-v3.pdf (visited on 2018-03-09).

[28] E. Haas, *Introduction to fhir*, Online Tutorial, 2016. [Online]. Available: https://gforge.hl7.org/gf/project/fhir/scmsvn/?action=browse&path=%2F%2Acheckout%2A%2Ftags%2F2016May%2Fpresentations%2F2016-01%2520Tutorials%2FIntroduction%2520to%2520FHIR-eh.pptx.

[29] R. Spronk. (2014). The early history of health level 7, [Online]. Available: http://www.ringholm.com/docs/the_early_history_of_health_level_7_HL7.htm (visited on 2018-03-19).

[30] Frank Oemig, *Interoperabilitätsforum Berlin*, personal communication, 2018.

[31] HL7. (2017). Resource Patient - Mappings, [Online]. Available: http://hl7.org/implement/standards/fhir/patient-mappings.html#http://hl7.org/v2 (visited on 2018-05-24).

[32] D. Bender and K. Sartipi, "HL7 FHIR: An agile and RESTful approach to healthcare information exchange", in *Proceedings of the 26th IEEE International Symposium on Computer-Based Medical Systems*, IEEE, 2013. DOI: 10.1109/cbms.2013.6627810.

[33] C. N. Mead, "Data interchange standards in healthcare it - computable semantic interoperability: Now possible but still difficult, do we really need a better mousetrap?", *Journal of Healthcare Information Management*, vol. 20, no. 1, 2006.

[34] Health Level Seven International. (2018). HL7 Version 3 Product Suite, [Online]. Available: http://www.hl7.org/implement/standards/product_brief.cfm?product_id=186 (visited on 2018-06-07).

[35] G. Grieve, E. Kramer, and L. McKenzie. (2012). Introduction to hl7 fhir, [Online]. Available: https://gforge.hl7.org/gf/project/fhir/scmsvn/?action=browse&path=%2F%2Acheckout%2A%2Fdstu2-last%2Fpresentations%2FIntroduction%2520to%2520FHIR.pptx (visited on 2018-05-21).

[36] HL7.org. (2017). Foundation Module, [Online]. Available: https://www.hl7.org/fhir/foundation-module.html (visited on 2018-04-10).

[37] ——, (2017). RESTful API, [Online]. Available: https://www.hl7.org/fhir/http.html (visited on 2018-07-01).

[38] ——, (2017). Messaging using FHIR Resources, [Online]. Available: https://www.hl7.org/fhir/messaging.html (visited on 2018-07-01).

[39] ——, (2017). Messaging using FHIR Resources, [Online]. Available: https://www.hl7.org/fhir/documents.html (visited on 2018-07-01).

[40] ——, (2017). Using Resources with Services and Service-oriented Architecture, [Online]. Available: https://www.hl7.org/fhir/services.html (visited on 2018-07-01).

[41] ——, (2017). Conformance Module, [Online]. Available: https://www.hl7.org/fhir/conformance-module.html (visited on 2018-04-10).

[42] SmartConData GmbH. (2018). HL7 FHIR, [Online]. Available: https://www.smartcondata.de/start/know-how/fhir-1/ (visited on 2018-06-03).

[43] TechTerms. (2018). Metadata, [Online]. Available: https://techterms.com/definition/metadata (visited on 2018-06-20).

[44] HL7.org. (2017). 5.1.0 profiling fhir, [Online]. Available: https://www.hl7.org/fhir/STU3/profiling.html (visited on 2018-04-06).

[45] ——, (2017). Profiling FHIR, [Online]. Available: https://www.hl7.org/fhir/profiling.html (visited on 2018-04-10).

[46] Simplifier.net. (2018). Profiling Academy, [Online]. Available: https://simplifier.net/guide/profilingacademy/modules (visited on 2018-06-03).

[47] M. B. Liu and K. Davis, *A Clinical Trials Manual from the Duke Clinical Research Institute*, 2nd. Wiley-Blackwell, 2010, pp. 53ff. ISBN: 1405195150, 9781405195157.

[48] U. D. of Health & Human Services. (). About clinical trials, [Online]. Available: https://www.nhlbi.nih.gov/health-topics/about-clinical-trials (visited on 2018-07-02).

[49] U. of California San Francisco. (2017). Clinical trial protocol development, [Online]. Available: https://hub.ucsf.edu/protocol-development (visited on 2018-06-21).

[50] A. Al-JunDi and S. SAkkA, "Protocol writing in clinical research", *Journal of clinical and diagnostic research: JCDR*, vol. 10, no. 11, ZE10, 2016.

[51] David Shoemaker, Karen Kesler. (2016). Protocol Design and Development: What You Need to Know to Ensure a Successful Study, [Online]. Available: https://www.youtube.com/watch?v=4UD8BlDLxxU (visited on 2018-04-28).

[52] R. Collier, *Legumes, lemons and streptomycin: A short history of the clinical trial*, 2009.

[53] vfa - Die forschenden Pharma-Unternehmen. (2018). Patienten in klinischen Studien, [Online]. Available: https://www.vfa.de/de/patienten/patienten-klinische-studien/klinische-studien.html/_4-warum-in-einer-studie-nicht-alle-gleich-behandelt-werden (visited on 2018-06-27).

[54] A. Bhatt, "Evolution of clinical research: A history before and beyond james lind", *Perspectives in clinical research*, vol. 1, no. 1, p. 6, 2010.

[55] Sandra Maddock. (2018). The History of Clinical Research, [Online]. Available: http://cdn2.hubspot.net/hub/149400/file-410979295-pdf/docs/CRT_Timeline_download.pdf (visited on 2018-06-12).

[56] Universität zu Köln. (2018). Medizinische fakultät - zentrum für klinische studien, [Online]. Available: http://zks.uni-koeln.de (visited on 2018-08-06).

[57] HL7.org. (2017). Resource researchsubject - content, [Online]. Available: http://build.fhir.org/researchsubject.html#statemachine (visited on 2018-08-08).

[58] Simplifier.net. (2018). Introduction to FHIR and profiling, [Online]. Available: https://simplifier.net/guide/profilingacademy/IntroductiontoFHIRandprofiling (visited on 2018-06-03).

[59] ——, (2018). Extensions, [Online]. Available: https://simplifier.net/guide/profilingacademy/Extensions (visited on 2018-06-03).

[60] ——, (2018). Slicing, [Online]. Available: https://simplifier.net/guide/profilingacademy/Slicing (visited on 2018-06-03).

[61] ——, (2018). Fhir registry, [Online]. Available: https://registry.fhir.org (visited on 2018-07-18).

[62] ——, (2018). Simplifier.net, [Online]. Available: https://simplifier.net/about (visited on 2018-07-18).

[63] ——, (2018). Best-practices, [Online]. Available: https://simplifier.net/guide/ProfilingAcademy/Best-practices (visited on 2018-06-03).

[64] U.S. National Library of Medicine. (2018). Sequential regimen of bendamustine-debulking followed by abt-199 and ga101-induction and -maintenance in cll (cll2-bag), [Online]. Available: https://clinicaltrials.gov/ct2/show/NCT02401503?cond=cll2-bag&rank=1 (visited on 2018-08-11).

[65] I. C. on Harmonisation Working Group *et al.*, "Ich harmonised tripartite guideline: Guideline for good clinical practice e6 (r1)", in *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*, Washington, DC., vol. 10, 1996, pp. 1–53.

[66] H. Leroux, A. Metke-Jimenez, and M. J. Lawley, "Odm on fhir: Towards achieving semantic interoperability of clinical study data", *The Australian E-Health Centre, Health and Biosecurity, CSIRO*, 2017-09.

[67] HL7.org. (2017). Resource researchstudy - content, [Online]. Available: https://www.hl7.org/fhir/researchstudy.html (visited on 2018-07-18).

[68] ——, (2017). Version management policy, [Online]. Available: https://www.hl7.org/fhir/versions.html (visited on 2018-07-23).

[69] ——, (2017). Resource plandefinition - content, [Online]. Available: https://www.hl7.org/fhir/plandefinition.html (visited on 2018-07-18).

[70] ——, (2017). Backboneelement, [Online]. Available: https://www.hl7.org/fhir/backboneelement.html (visited on 2018-07-29).

[71] ——, (2017). Resource activitydefinition - content, [Online]. Available: https://www.hl7.org/fhir/activitydefinition.html (visited on 2018-07-19).

[72] ——, (2017). Resource medicationrequest - content, [Online]. Available: https://www.hl7.org/fhir/medicationrequest.html (visited on 2018-07-21).

[73] ——, (2017). Resource medicationstatement - content, [Online]. Available: https://www.hl7.org/fhir/medicationstatement.html (visited on 2018-07-21).

[74] ——, (2017). Resource encounter - content, [Online]. Available: https://www.hl7.org/fhir/encounter.html (visited on 2018-07-21).

[75] Health Samurai. (2018). Simplifying development of interoperable healthcare solutions with a fhir backend, [Online]. Available: https://www.interoperabilityshowcase.org/sites/interoperabilityshowcase/files/himss_white_paper_-_health_samurai.pdf (visited on 2018-08-02).

[76] Grahame Grieve. (2018). Active Questionaires in #FHIR, [Online]. Available: http://www.healthintersections.com.au/?p=2835 (visited on 2018-07-19).

[77] Simplifier. (2018). Patient, deutsches Basisprofil (Version 0.2), [Online]. Available: https://simplifier.net/basisprofilde/patient-de-basis-0.2 (visited on 2018-07-01).

[78] ——, (2018). nl-core-patient, [Online]. Available: https://simplifier.net/nictizstu3-zib2017/nl-core-patient (visited on 2018-07-01).